Experience-based specialisation: underpinnings of communication in typical and atypical development

Experience-Based Specialisation: Underpinnings of Communication in Typical and Atypical Development

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Originality Statement

'I, Anna Kolesnik, hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the University of London or any other educational institution, except where due acknowledgment is made in the thesis. Any contribution made to the research by others, with whom I have worked at University of London or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.'

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Findings from Eye tracking Task 1 (Chapter 3) are currently in preparation for submission by **Kolesnik, A**., Del Bianco, T., Quiroz, I., Mason, L. and Jones, E.J.H.; titled '*Age and language experience effects on active seeking of native language in pre-verbal infants*'.

A portion of the work presented in EEG Task 2 (Chapter 5) appeared in article: **Kolesnik, A**., Begum Ali, J., Gliga, T., Guiraud, J., Charman, T., Johnson, M.H. and Jones, E.J.H., '*Increased cortical reactivity to repeated tones at 8 months in infants with later ASD*' (adaptations to this chapter included additional analysis of ERP data as well as Change Detection as well as removal of content added by collaborators on the paper). In addition, part of the pre-processed data was also used in a dissertation project for Cognitive Neuroscience and Neuropsychology MSc (Birkbeck College) "*Gamma-band oscillations as a biomarker of*

Excitation/Inhibition imbalance in infants with high risk of Autism Spectrum Disorder" submitted on August 2016. Note that since submission data processing and analysis pipeline has been substantially expanded and modified.

Abstract

Autism Spectrum Disorder (ASD) is an umbrella term encompassing several neurodevelopmental conditions with complex, heterogeneous symptomatology. One way in which I addressed this complexity is by looking at a specific aspect of the phenotype to understand the contributing mechanisms. Communication difficulties are prevalent in ASD, and it has been suggested that this is a downstream effect of atypical functional specialisation in processing of both social and non-social auditory input in the brain. This thesis aimed to identify robust markers of specialisation across several methodologies and assess the links with the behavioural phenotype. First, a series of eye tracking studies was carried out with typically developing infants to identify age and language experience effects on speech perception and whether these can be linked to brain-based markers of specialisation. Then, three auditory EEG paradigms were used to measure differences in auditory perception in infants with increased familial likelihood of ASD and/or ADHD, as well as in a unique population of infants with NF1, who experience elevated rates of ASD and other neurodevelopmental conditions as part of the clinical symptomology. Through inclusion of several different participant groups, it was possible to examine whether atypical auditory processing was a specific marker of familial and/or monogenic likelihood of ASD or a general predictor of atypical development.

Chapter 2 outlined the main techniques used to measure experience-dependent specialisation, including eye tracking, EEG and behavioural assessments. ***Chapter 3*** investigated specialisation towards native speech perception though several novel paradigms in a longitudinal sample of neurotypical infants at 5, 10 and 14 months of age, as well as associations with parent and observer-rated language abilities. ***Chapter 4*** examined the relationship between eye tracking, neural indices of vowel perception and communication skills in neurotypical infants and how these EEG-based indices may differ in a group of infants with NF1 at 5 and 10 months. ***Chapter 5*** investigated differences in neural habituation and

change detection responses across time and time-frequency analyses in 8-month-old infants with low and high familial likelihood of ASD and how these relate to language and ASD symptomology at three years. Lastly, ***Chapter 6*** examined steady-state responses in the gamma frequency range in 14-month-old infants and whether this auditory marker can be used to differentiate between neurotypical infants and those with familial likelihood of ASD or ADHD or an NF1 diagnosis and to predict individual differences in communication skills.

Taken together, the present work explored early markers of functional specialisation of auditory processing in typical and atypical development in association with parent/observer ratings of early language ability. Additionally, findings are reported from the first study of early brain development in infants with NF1. This is integral to the current understanding of pathways to ASD, with a further aim of informing clinical and research practices in rare genetic disorders.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ALE	Additional Language Experience
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor or quisqualate receptor
AOI	Area of Interest
ASD	Autism Spectrum Disorder
CDI	MacArthur Bates Communicative Development Inventory
E/I	Excitation/Inhibition Balance
EEG	Electroencephalography
ERP	Event-Related Potential
ETM	Eye-to-Mouth Looking Ratio
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
GABA	*gamma*-Aminobutyric acid
LMM	Linear Mixed Model
LT	Looking Time

MEG	Magnetoencephalography
MRS	Magnetic Resonance Spectroscopy
NF1	Neurofibromatosis Type 1
NMDA	N-methyl-D-aspartate
PD	Pupil Diameter
STS	Superior Temporal Sulcus

Chapter 1. General Introduction

1.1 Specialisation of Communication and Language in the First Years of Life

Infants show early communicative behaviours from just a few hours after birth that include crying and enhanced attention to faces, which progress into babbles, jabbering and joint attention. Then, follows the emergence of their first recognisable word around the end of the first year of life. Infants quickly become experts at navigating the social world, and looking at perception of incoming auditory information is perhaps one of the most direct ways in which this process can be studied. Over a relatively short time, infants become specialised to processing the nuances of their native language and non-verbal communication. Recent decades have seen increased interest in identifying the underlying brain mechanisms and their relationship to the behavioural changes that precede the onset of the first word.

For the purposes of this work, only the speech perception aspect of communication is focused on, rather than the emergence of language structures. One of the most pertinent theories of early child development is based on a domain-general framework of human evolution, which suggests that communication and adult levels of speech processing are attained through increased cortical specificity and a dynamic relationship between the child and their environment (Johnson, 2011; Johnson, Halit, Grice, & Karmiloff-Smith, 2002). Although more recent lines of evidence question whether speech and language acquisition are 'biologically special' in comparison to other early skills, it remains one of the fundamental aspects of human communication. Therefore, I investigated the age-dependent functional changes that occur within auditory processing in the brain and whether basic behavioural or neural indices of speech and non-speech processing that can predict key language milestones in the first year of life. Further, I questioned: are these brain markers sensitive to early differences in neural

specialisation in cases of atypical development and in the wider context of neurodiversity? What is the role of individual experience?

Autism Spectrum Disorder (ASD) is an overarching term for a heterogeneous behavioural phenotype with several different causal pathways and is diagnosed from around 3 years of age through behavioural assessments. It is defined through difficulties in social communication, as well as the presence of restrictive and repetitive behaviours (DSM-5; American Psychiatric Association, 2013). It has been established that language and communication problems are prevalent in in ASD and this constitutes a major part of the diagnostic criteria in clinical settings.

Children with ASD have shown marked deficits in understanding and producing language (Charman et al., 2003; Howlin, 2003; Koning & Magill-Evans, 2001), with 10% never developing functional language skills (Hus et al., 2007). There is still very little known about the underlying mechanisms of language impairment, however (Guiraud et al., 2012), and the recent surge towards finding a 'biomarker' of ASD is yet to yield conclusive results (Kapur et al., 2012). The difficulty in isolating a single marker predictive of ASD diagnosis may be due to the heterogeneity and complexity of the phenotype, which challenges the categorical approach to diagnosis of neurodevelopmental conditions.

Based on the recent initiative 'Research Domain Criteria' (RDoC) by the National Institute of Mental Health (HIMH), I take a dimensional approach to understanding developmental disorders and use auditory processing as a measurable aspect of the phenotype. This is fundamental for understanding communication abilities in ASD and the broader ASD phenotype (Cuthbert & Insel, 2010, 2013; Foss-Feig et al., 2016), and using this approach allows to map out the functional spectrum of speech processing in infancy. A dimensional approach further allows to address the question of whether these difficulties are syndrome

specific to ASD or whether they represent a common pathway of 'atypical' neurodevelopment present across monogenic and developmental conditions.

Early markers predictive of ASD have been detected in the first 12 months of life, e.g. through a decline in attention to faces between 2 and 6 months of age (Jones & Klin, 2013a) or reduced audiovisual speech cues (Guiraud et al., 2012). It has also been reported that infants who go on to receive an ASD diagnosis in childhood, show atypical auditory processing behaviours in infancy and poorer language outcomes relative to their neurotypical peers (Linke et al., 2018; Port et al., 2017; Rojas et al., 2011). As such, possible dysregulation within the functional specialisation of auditory processing mechanisms (both speech and non-speech sounds) may be present alongside social and sensory processing atypicalities. Identifying brain-based indices of auditory perception will enable better predictions of language outcome to be made in populations with elevated likelihood of neurodevelopmental conditions, which could aid the design and administration of targeted treatments. By looking at neurodevelopmental disorders that also present with language difficulties, it is possible to examine similarities and differences across early neurophysiological and behavioural responses to the environment in order to understand the existing paths to communication abilities in the brain.

In addition to exploring auditory processing in idiopathic ASD, I investigated the similarities and differences in infants with a diagnosis of the monogenic disorder Neurofibromatosis Type 1 (NF1) and family history of Attention Deficit Hyperactivity Disorder (ADHD). Due to high levels of heterogeneity in the idiopathic ASD sample, it is difficult to isolate factors that have specific effects on ASD symptomology. By looking at several different conditions with overlapping symptomatology, effects of genetic and environmental contributors can be examined, as well as understanding of the different pathways to subsequent emergence of ASD. Moreover, the findings reported in this thesis come from the first known investigation of development in NF1 in the world and therefore offer a

unique insight into the early effects of the condition on the brain in this population. This is highly important for both populations as there is an equally limited conception of the factors that influence the elevated incidence rates of neurodevelopmental conditions in known genetic disorders.

To understand the differences in the overall communication and auditory processing in infants with familial or monogenic likelihood of neurodevelopmental disorders, the paths to language in typically developing infants must be considered according to the currently available theories of functional brain development. Several investigations have looked at developmental increases in the volume and functionality of language-related networks across childhood and early adulthood and found evidence of specialisation to adult-like levels of proficiency (Battista et al., 2018). Many recent studies have also addressed age-dependent changes in auditory perception (Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002; Kushnerenko, Bergh, Bea, & Winkler, 2013) and the narrowing towards native vs. non-native languages (Bosseler et al., 2013; Elsabbagh, Hohenberger, et al., 2013) using a range of behavioural and neuroimaging methods.

For example, there is evidence that discrimination of speech sounds from as early as 7 months is predictive of language abilities at 2–3 years (Rivera-Gaxiola et al., 2005). Additionally, there is increased discrimination of speech sounds during the first year of life, with emerging perceptual narrowing towards the native language at around 10 months of age (Werker & Polka, 1993). The latter has also been shown to be influenced by the type of language sounds that are heard in the infant's early environment (Kuhl et al., 2008). There is limited research looking at the relationship between looking behaviour and the neural indices of specialisation, which was addressed in the present work.

It should be noted that by the age of 3, when an ASD diagnosis can be made by a clinician, many of the early processes of functional specialisation have already taken place.

Most children experience a growth spurt in their vocabulary and grammar between 16 and 24 months (i.e. up to 2 years; Bates et al., 1992) and difficulties in speech and language processing manifest on a phenotypic level.

There are no distinct markers that have been attributed to the process of early functional specialisation to human speech, and there is little understanding of individual variability in both typical and atypical development. By investigating preverbal representations of speech and non-speech sounds in the brain, it will be possible to understand how interactions within comparatively unspecialised regions at birth produce a system that is ready for comprehension and production of a 'native' language. This can further help with early detection and construction of individualised treatment protocols for infants who do not show these early speech processing capabilities and may therefore have a higher likelihood of language difficulties in childhood.

One of the questions posed by the literature is how is specialisation manifested during the first years of life and how can behavioural and electrophysiological markers be used to predict developmental outcomes. The primary focus of this thesis has been to identify the brain markers of specialisation within neurocognitive networks during auditory processing and how these markers change over time and across alternative developmental trajectories. Additionally, I looked at the relationships between neurophysiological and cognitive correlates of early communication in infancy and toddlerhood. The 'final state' of language acquisition in the mature brain and what is associated with communication in human adults (e.g. grammar, syntax and semantics) is beyond the scope of this work.

1.2 Theoretical Perspectives on Brain Maturation and Acquisition of Auditory Processing Expertise in Typical Development

To formulate more specific hypotheses about early specialisation towards communication in infancy, three main theories of development were considered, including Maturation, Experience and Interactive Specialisation, all of which are domain-general frameworks. This means that each framework aims to explain findings across a broad range of infant skills and abilities through a specific set of predictions and constraints.

There are two overall approaches that can be taken in the study of early development that must be acknowledged (Gottlieb, 2002): predetermined epigenesis and probabilistic epigenesis. Predetermined epigenesis argued that maturation of particular pathways or regions enables specific functions to appear, which means that changes in cognition are the direct outcome of brain maturation (Diamond, 1991; Johnson, 1990). This is consistent with the Maturation theory in outlined in Chapter 1.2.1.

Alternatively, probabilistic epigenesis (Gottlieb, 2007) suggests that there are ongoing interactions between genes, brain structure, the environment and psychological changes that are bidirectional. Activity-dependent development appears as the integral component of this approach, where infants are actively choosing the appropriate input that guides further specialisation (see Figure 1.1). This theory closely resembles the predictions made by the interactive specialisation framework discussed in Chapter 1.2.3. At present, there is limited understanding of the bidirectional relationship between brain structure and function, therefore, understanding of cognitive development becomes more complex. This is key when thinking about mechanisms of neural specialisation over time.

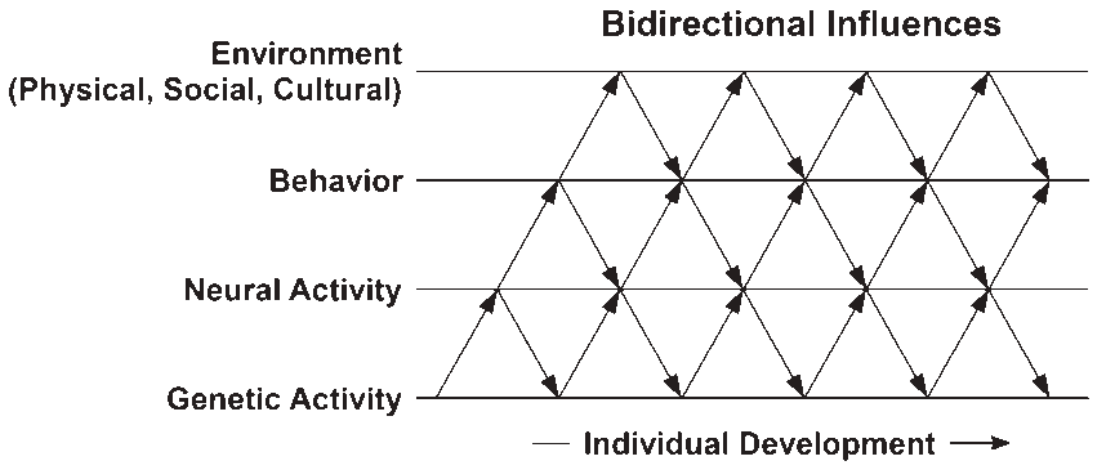

Figure 1.1 Metatheoretical model of probabilistic epigenesis (Gottlieb, 1992). Note the relationships between different systems and their bidirectional nature. This aims to more accurately represent the dynamics of early human development.

1.2.1 Maturational framework.

To date, much of the research available on early brain development has focused on relating the findings regarding early infant abilities to skills are known to exist in the adult brain. This theory argues that 'maturation' of given regions of the brain facilitates the emergence of sensory, motor and cognitive abilities. It further quantifies success in any given experimental task as an indicator that the associated brain region has reached maturity. The theory states that development of specific regions of the brain is predetermined through genetic, biochemical and neuroanatomical factors. A disruption within any of the relevant processes would therefore reduce or eliminate the expected function of the region.

This somewhat extreme view, which heavily relies on assumptions of the nature rather than nurture aspect of human development, suggests that there is a range of innate structures in the infant brain that facilitate the emergence of specific skills, including communication, i.e. language comprehension and production (Chomsky, 1972, 1986). For example, it has been

argued that early damage to 'perisylvian areas of the left hemisphere'[1] impairs the acquisition of language (Dennis & Whitaker, 1976; Raja Beharelle et al., 2010; Vargha-Khadem et al., 1994). Findings regarding focal damage to the left hemisphere and poorer language outcomes, as well as an apparent left hemisphere bias in language processing studies led to the early conclusion that functional localisation of communication and language abilities is established at birth and cannot be reversed in later life (Minagawa-Kawai et al., 2011; Shultz et al., 2014).

1.2.1.1 Evidence for/against maturational framework.

Several studies have presented brain imaging evidence to suggest 'innate' localisation of a given function in the infant brain that corresponds to the location of that function adulthood. Left and right hemispheric differences have been noted in auditory processing from as early as the foetal period into early infancy (Dehaene-Lambertz, 2000; Dehaene-Lambertz et al., 2010; Ghislaine Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Homae, Watanabe, Nakano, & Taga, 2011; Mahmoudzadeh et al., 2013; Shultz et al., 2014; Vannasing et al., 2016). Animal and human imaging studies revealed that responses to native, non-native and backwards speech are more lateralised to the left hemisphere compared to other vocal sounds (see Shultz et al., 2014 for review). The evidence was used to support the maturational framework as the left hemisphere is associated with language processing in neurotypical adult brains (Molfese, 1973; Molfese et al., 1975; Whitehouse & Bishop, 2008). However, protracted development of left hemisphere lateralisation (Szaflarski et al., 2006) and differences in adult

[1] Perisylvian language zone covers the region around the lateral sulcus/Sylvian fissure of the left hemisphere and includes Broca's area, Wernicke's area, which are thought to be connected by two parallel pathways (Catani et al., 2005).

lateralisation based on handedness question the validity of hemispheric bias for language processing (Knecht et al., 2000; Steinmetz et al., 1991).

Additionally, location of neural responses to speech stimuli have been found to vary by context. Right or left hemispheric bias was reported if adults were asked to pay attention to vowel identity or to voice pitch, respectively (Zatorre & Belin, 2001). Right hemisphere bias towards music was observed by Perani and colleagues (2010), but not by Dehaene-Lambertz and colleagues (2010), where both speech and music stimuli were used. Another study with 2-day-old infants showed that there were functional and structural connections within the fronto-temporal network associated with language processing, although strong connections appeared only between the left and right hemisphere rather than within (Perani et al., 2011). Authors also found that there was higher activation of BOLD response[2] towards normal speech in the right hemisphere. Overall, recent imaging suggest that while maturation is an important contributor to obtaining adult-like levels of proficiency in speech and language processing, study context and infant's individual level of language experience is more predictive of language and communication ability (Perani et al., 2011).

Pujol and colleagues (2006) reported cross-sectional findings from a three-dimensional magnetic resonance imaging (MRI) study that measured volume of myelinated white matter in language-related frontal and temporal regions. It was found that comprehension and production networks had similar courses of myelination development. When the rapid myelination phase was complete, around 18 months of age, a large acceleration was also observed in the child's

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[2] Blood-oxygen-level-dependent imaging/BOLD contrast imaging is a method used in functional magnetic resonance imaging (fMRI), where higher responses suggest a higher hemodynamic response due to increased metabolic demand of the area.

vocabulary (Pujol et al., 2006). The observed relationship was used to support the maturational framework, as the 'onset' of spoken language coincided with sufficient functional development of the relevant regions.

A study using magnetoencephalography (MEG) also showed increases in auditory processing efficiency as a function of age in children aged between 6 and 59 months (i.e. up to five years old; Edgar et al., 2015). The paradigm involved simple auditory frequency stimuli and revealed effects of age on speed of processing, with older infants showing gradually quickening response latencies to auditory stimuli in the left hemisphere. The result was further supported by functional frontal lobe activation being observed in young infants, albeit in an immature state. As such, the adult equivalent of the P300 was recorded between 700 milliseconds (ms) and 1 second (s) until the end of the first year of life, and it was suggested that there is an innate function for the processing of auditory stimuli in that region, although maturation is critical to achieve adult-like proficiency (Kouider et al., 2013). However, the large majority of studies that support the maturational framework take the cross-sectional approach, i.e. assess different groups infants at two or more predetermined age points, which does not allow for the assessment of individual variability in the early development of a given skill.

1.2.1.2 Maturational framework: typical vs. atypical development.

Next, the limitations of the maturational framework are considered in relation to current research, in addition to findings from atypical development and neurodevelopmental disorders. The theoretical framework is a reductionist view of the brain that assumes concepts of plasticity and cortical reorganisation as additional mechanisms of development rather than its driving forces. It is difficult to reconcile the assumptions of this framework based on what is known about early brain development, particularly the variability in time and location of early changes. For example, functional asymmetry has been observed during the neonatal period in

several studies and has been recognised as the fundamental architecture that allows infants to learn language (Dehaene-Lambertz, 2017). This has been combined with other lines of evidence to suggest that representation of language regions in the cortex is not endemic to the left hemisphere.

The maturational account further fails to acknowledge differences between the established neural systems observed in adult neuropsychology and those of young infants (Karmiloff-Smith, 2009, 2013). Focal brain damage studies in infants have shown across- and within-hemispheric reorganisation that is able to support relatively normal language function in childhood, however (Guzzetta et al., 2008; Liégeois, Mayes, & Morgan, 2014; Reilly, Bates, & Marchman, 1998). It has also been found that the regions of the brain usually associated with language can also support other functions in congenitally Deaf children and adults (Bavelier & Neville, 2002; MacSweeney et al., 2008).

Although supporters of the maturational framework have acknowledged that experience does have a role in development (Segalowitz & Rose-Krasnor, 1992), the direction of this relationship and the interaction with biological factors is not specified. The framework also fails to adequately conceptualise atypical neural development and neurodiversity (Karmiloff-Smith, 2013). Previous investigations based on the maturational framework have suggested that developmental conditions such as ASD are due to a deficit in the 'theory of mind' (ToM) module (Baron-Cohen et al., 1985; Leslie, 1992; Scholl & Leslie, 1999). Baron-Cohen and colleagues (1985) conducted the seminal behavioural investigations in which children with ASD failed to conceptualise knowledge from another person's viewpoint relative to their neurotypical peers and those diagnosed with Down Syndrome. This led to the conclusion that ASD is a ToM deficit.

Replications of this study design have reported associations between ToM task performance and verbal ability (Astington & Jenkins, 1999; Happé, 1995; Sparrevohn &

Howie, 1995), which suggested that differences reported originally may be accounted for by task difficulty and reliance on comprehension of verbal instructions. More recently, the idea of ASD as a ToM deficit has been questioned in the literature as there are no cases of ASD where only the ToM module is impaired in the context of an intact neural system (Stone & Gerrans, 2006). Indeed, individuals with focal damage to the proposed brain regions that hold the ToM, namely the orbitofrontal cortex and the temporal parietal junction, also tend to have difficulty recognising facial expressions and processing eye gaze information in absence of characteristic ASD symptomology (Gregory et al., 2002; Stone, Baron-Cohen, & Knight, 1998). The findings indicate that ToM is a skill that cannot be impaired in isolation.

Additionally, ToM is thought to emerge between 3 and 5 years, whereas there is substantial evidence to suggest that physiological and behavioural markers predictive of the ASD phenotype are present in the first year of life. These arguments also apply to the theory of 'frontal lobe dysfunction' as an explanation for difficulties in social processing (Grattan & Eslinger, 1992). It is difficult to isolate specific skills or regions as being 'impaired' in development without secondary consequences for the whole brain and this theory further fails to account for the vast heterogeneity present within the ASD phenotype.

Another assumption that is challenged by recent findings is that a *single* gene can give rise to a specific behaviour or cognitive outcome[3]. The idea has been discredited through

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[3] The FOXP2 gene became one of the most prominent candidates and was reported in several generations of a family who showed language impairments specific to grammar (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). The difficulties associated with this mutation also included low general intelligence, language difficulties beyond grammar and coordination of simple mouth movements, however (Alcock, Passingham, Watkins, & Vargha-Khadem, 2000; Vargha-Khadem et al., 1998).

genetic studies that suggest that it is a much more complex interaction between many different genes that increases the likelihood of a certain skill or behaviour emerging. This is particularly true for genetic disorders like Williams Syndrome, Fragile X as well as ASD and ADHD, where there have been several unsuccessful attempts to link deletions/multiplications in single gene regions with phenotypic outcomes (Bellugi et al., 1999; Dahlhaus, 2018; Faraone & Larsson, 2019; Grove et al., 2019; F. G. E. Happé et al., 2006; Karmiloff-Smith, 2006; Karmiloff-Smith et al., 2012; Nikitina et al., 2014).

Recent advances in the fields of genetics and epigenetics have revealed dynamic and complex interactions between the genes and environment. In neurodevelopmental disorders such as ASD, over 100 candidate genes have been identified to date that can facilitate a molecular diagnosis in 5–40% of ASD cases (Iossifov et al., 2014; Jensen & Girirajan, 2017; Kosmicki et al., 2018; Marshall et al., 2008; Satterstrom et al., 2018). These genes do not act in isolation, however, which means that isolating specific 'risk genes' has limited clinical utility.

Overall, it can be argued that the maturational framework highlighted the importance of early development and led to the idea of 'critical periods', which is still widely investigated today. However, the assumptions behind the framework are somewhat reductionist and diminish the importance of plasticity, individual variability and the influence of environmental factors in driving maturation.

1.2.2 Experience framework.

Another widely applied theoretical framework of infant brain development states that the processing of stimuli from the external environment, as well as the development of all other skills and abilities, is a product of interactions between the basic mechanisms of learning and skill acquisition with the environment. The experience framework argues that the development

of brain functions (excluding mechanisms that facilitate learning itself) is driven by experience and that skills are learnt through interaction with the environment rather than being innately specified by the genome. While the types of skill learned may differ with age, e.g. basic sensory and motor abilities in infancy and more complex cognitive skills, such as language and metacognition in adulthood, it is assumed that acquisition of these skills is identical across all ages.

One of the most common abilities explained by the experience theory is that of face processing. It is believed that cortical specialisation for faces is driven by the experiences of the visual system, with certain regions being particularly suited for fine-tuned processing of individual features (Gauthier, Skudlarski, Gore, & Anderson, 2000; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999).

It has been suggested that areas in the ventral temporal regions, such as the fusiform gyrus (also termed the fusiform face area or the FFA) become increasingly tuned to the discrimination of faces with increasing age/experience (Gauthier et al., 1999; Kanwisher & Yovel, 2006; Tarr & Gauthier, 2000). There is evidence for higher levels of specialisation towards native versus non-native faces (Michel et al., 2006) and other non-face objects of expertise, which elicit comparable neural responses (Bilalić et al., 2011; McGugin et al., 2012).

Although some studies of new-borns have suggested that face processing is experience independent (Morton & Johnson, 1991), it could also be argued that neonates receive sufficient experience in the few hours/weeks after birth with the caregiver to develop a preference towards face-like stimuli. Other studies have not shown this innate 'preference' between intact and scrambled face stimuli (Easterbrook et al., 1999), which led to the conclusion that there may be methodological differences that account for the neonate face-preference effect. It was also found that older infants show different patterns of activation to faces than objects, which

emphasised the effect of experience with faces in shaping neural processing (de Haan & Nelson, 1999).

The finding that experts in birds or cars also show FFA activation when presented with images from their area of expertise (Gauthier et al., 2000) argued against the concept of an innate 'module' and domain specificity that lie at the centre of the maturational framework, as discussed in the Chapter 1.2.1(Coltheart, 1999; Fodor, 1983). Gauthier and Nelson (2001) also provided experimental evidence of adults achieving high levels of expertise in the discrimination of non-face objects following extended periods of training in a laboratory environment used in the development of the experience framework.

Moreover, face-like processing networks were found to be activated when discriminating between cats, birds and dogs and Greebles[4] (Diamond & Carey, 1986; Gauthier et al., 1999; Tarr & Gauthier, 2000), which suggests that months or years of visual experience are not necessary to activate this processing stream and that face expertise can be shown for non-face objects. An additional strength of this research is that Greebles were unfamiliar objects, which meant that the individual levels of experience were controlled (relative to studies of experts in animals/objects); although the environmental validity of this type of learning can be questioned.

1.2.2.1 Evidence for/against experience framework.

One of the key limitations of this framework is that it fails to account for infants' innate abilities, including preferential processing of faces from as early as 9 minutes after birth (Goren

[4] Invented category of novel objects used in adult psychological studies of object and face recognition that can be divided into two genders and five families (Gauthier & Tarr, 1997).

et al., 1975). Although it could be argued that an infant hears their mother's voice in the womb, which provides them with auditory experience that results in preference, infants do not have experience with faces and therefore learning alone cannot account for this phenomenon. There is also evidence to suggest that infants process face objects differently to non-face objects by around 6 months of age, which assumes that all infants would have similar levels of experience with faces (de Haan & Nelson, 1997, 1999).

It has been argued that infants have innate learning mechanisms specific to faces that accelerate this process relative to perception of non-face objects as infants showed a preference for configural images of faces based on stimuli previously viewed for <1 second relative to novel stimuli (Walton & Bower, 1993). Due to methodological limitations, however, including the use of cross-sectional design, it cannot be established whether this ability is due to (1) increased experience with faces compared to objects or (2) if there is an experience-independent process that drives this face-selectivity. There are inconsistencies in previous research, as the face preference was not observed in infants at 2 months of age (Morton & Johnson, 1991). As such, it is necessary to look at specialisation of social communication mechanisms through prospective, longitudinal designs to understand the role of experience versus innate biological factors in driving developmental change.

More specific to this project, experience framework has also been applied to communication and speech processing, with the results suggesting that preference towards native speech is acquired from interactions with the environment. Early responses to speech vs. non-speech sounds in neonates has been attributed to auditory experience with their mothers' voices in the womb (Easterbrook et al., 1999; Kisilevsky et al., 2003; Mampe et al., 2009). Additionally, experience is thought to be integral for speech perception and subsequent production as it allows categories to be built for incoming speech stimuli, thereby ensuring faster recognition (Kuhl, 1993; Vallabha, McClelland, Pons, Werker, & Amano, 2007). The

existence of these native language categories have been reported in infants from 6 months of age using passive listening paradigms (Burns, Werker, & Mcvie, 2003; Kuhl, Williams, Lacerda, Stevens, & Lindblom, 1992; Teinonen, Aslin, Alku, & Csibra, 2008). Werker and Curtin (2005) proposed a developmental model that links early speech perception to later language acquisition and production. The PRIMIR (Processing Rich Information from Multidimensional Interactive Representations) model assumes that there is rich information embedded in speech input that the child is able to recognise and, with the help of 3 dynamic filters/biases that direct infant attention, organise information to formulate accurate representations of the native language (Werker & Curtin, 2005). Specifically, the model addresses the non-linear advancement in language learning, with the attentional filters (initial biases, task demands, and developmental level), becoming less important over developmental time. An overall importance of the model is that it forms closer associations between speech perception and subsequent word learning, which is explored throughout the course of this work. The model is supported by experimental findings from the same research group, i.e. 14-month-old infants with bigger vocabularies were better able to use phonetic detail to learn new words (Werker et al., 2002; Beckman & Edwards, 2000). This is further supported by adult neuroanatomical models of speech perception (Hickok & Poeppel, 2000; Scott & Wise, 2004; Wong et al., 2010). The model, however, assumes the existence of innate biases, which are not fully justified (Werker, 2018; Werker & Curtin, 2005). It should be noted, that there is large variability in the methods used across these studies and that there are large gaps in the understanding of markers of auditory processing and the potential individual variability that is central to capturing typical and atypical development.

An important concept emerging within language acquisition is the idea of ‘critical periods’, which was originally proposed by Lenneberg (1967). The theory largely applied to infants’ learning of their first language. Since then, the notion of critical periods has been

extended to second language acquisition (Johnson & Newport, 1989; Singleton & Lengyel, 1995), supported by the finding that exposure to a second language was negatively correlated with the average degree of perceived accent in children (Flege et al., 1995). It was suggested that infants have to receive quality verbal input and that this could be used to predict proficiency. Kuhl (2007) further argued that experience with the social world is necessary to move from universal processing to language-specific processing, which highlights the importance of experience in gaining expertise in both social and verbal communication. The finding that gaze following in preverbal infants was related to language outcomes at 1.5 years further supported the idea of critical periods for different stages of language acquisition (Brooks & Meltzoff, 2005).

However, learning alone cannot account for the speed and specificity with which infants acquire skills and abilities, and maturational processes within the brain have a profound effect on acquisition (Johnson & Newport, 1989). It should be noted that experiential effects are mainly reported for the processing of basic language features, such as sound discrimination rather than higher order processes including syntax and vocabulary. The complexity of languages has led researchers to argue that learning and experience alone cannot account for the speed and proficiency with which infants acquire their native language within the first few years of life (Boeckx & Longa, 2011).

1.2.2.2 Experience framework: typical vs. atypical development.

Based on the assumptions of this framework, atypical development is regarded as a failure of learning mechanisms to attend and extract the necessary information from the environment, which gives rise to a specific behavioural phenotype and reveals different patterns of expertise relative to neurotypical peers. Failure to attend to social stimuli has been used as a common argument underlying atypical processing of social stimuli and communication in ASD (Bottini, 2018; Chevallier et al., 2012). It has been suggested that due

to a lack of social motivation, individuals with ASD do not engage with the social aspects within their environment and therefore do not develop the same level of expertise in areas of social communication, including face processing and language. As well as reduced/absent expertise towards facial configurations, some studies found hypoactivation of the FFA in ASD (Grelotti et al., 2005; Hadjikhani et al., 2007; Hubl et al., 2003; Pinkham et al., 2008; Schultz, 2005), which supported the assumption that the 'face region' does not receive a sufficient amount of experience and is therefore unspecialised.

A small-sample fMRI study found that face processing occurs outside the FFA in ASD, however, with each individual revealing a unique neural circuitry during a face perception task (Pierce et al., 2001). The finding is consistent with concepts of brain plasticity and functional reorganisation in infancy (Chugani et al., 1996; May et al., 2011; Vicari et al., 2000). Furthermore, it highlights the complexity of the causality debate for the observed face processing deficit within the FFA, i.e. whether the FFA fails to develop due to differences in social motivation or due to dysregulation within the underlying biological mechanisms.

Difficulties in communication and language are established characteristics of the ASD phenotype. Based on the experience framework, these difficulties can also be attributed to a lack of interest in communication, which reduces the infant/child's seeking behaviours and results in reduced verbal input and reduced specialisation towards the native language (Kujala et al., 2013). There are several studies that show atypical speech and non-speech auditory perception in ASD (Galilee, Stefanidou, & McCleery, 2017; Guiraud et al., 2012; Jones, Venema, Earl, Lowy, & Webb, 2017; Orekhova et al., 2008, 2012; Seery, Tager-Flusberg, & Nelson, 2014). There is also evidence to suggest that females with ASD, who generally present with better language outcomes than males, show enhanced social attention to speaking faces, which may act as a protective mechanism for some of the more severe aspects of the symptomology (Chawarska et al., 2016).

Reviews of the literature found no overall differences in social attention between children with ASD and neurotypical peers, however (Falck-Ytter & von Hofsten, 2011; Guillon et al., 2014), and one prospective study found equal levels of sustained attention to faces in infants during a passive viewing task (Elsabbagh, Gliga, et al., 2013). The reports question the theory that ASD is a direct result of inattention and avoidance of social information. As such, there is little consistent evidence that levels of experience can predict language outcomes during the preverbal stages of development nor to account for the large amount of variability that is seen in communication and language skills in children and adults with ASD.

Another important limitation of the experience framework is that learning is assumed to be an analogous process between infants and adults. Several studies found more extensive and pervasive effects of brain injury with age (Kolb & Whishaw, 1989; Teuber & Rudel, 1962), as well as poorer second language acquisition (Johnson & Newport, 1989), with younger ages showing higher success rates for the latter. Assuming all skills are inherently learned through experience also limits the role of biological factors and attributes a minimal role of familial or genetic influences on phenotypic expression. The PRIMIR model discussed above, offers a scaled learning model, where certain biases are prevalent for guiding attention based on developmental stages. It is therefore suggested that developmental delays associated with conditions such as ASD and ADHD may have an impact on directing the child's attention (i.e. developmental level of the child as one of the three developmental filters). This is supported by the finding that children with ASD are less sensitive to human voices, directing less attention over time than typically developing infants. The initial failure to attend to speech has downstream effects on social-communication skills, consistent with the timing of symptom emergence in ASD (Haesen et al., 2011; Sperdin & Schaer, 2016). A behavioural study has shown superior speech processing in children with ASD, where distinct preference was observed for perceptual (intonation) than linguistic (semantic) information relative to age and

IQ-matched controls (Järvinen-Pasley et al., 2008). Notably, children with ASD preferentially responded to word meaning in 65% trials (vs. 94% in the TD population), which suggested that processing of semantic information is not fully impaired (Happé & Frith, 2006), which supports the assumptions of the PRIMIR model. Yet, prospective longitudinal studies using this model in neurodiversity populations are necessary to substantiate its assumptions.

Overall, it could be argued that the experience framework has been critical in shifting the deterministic mind-set of maturational accounts of development and illuminated the importance of experience in the construction of processing expertise across many modalities. Current research suggests that biological factors drive some early learning mechanisms, however, and must be accounted for when describing the full complexity and diversity of development.

1.2.3 Interactive Specialisation framework.

In contrast to the frameworks discussed above which lie on opposing sides of the nature vs. nurture debate, the Interactive Specialisation (IS) framework assumes that postnatal brain development occurs through a process of self-organisation within the brain that is impacted by both age and activity-dependent processes (Johnson, 2000, 2011). The framework argues that cortical regions start off with a relatively wide range of functionality and that activity-dependent interactions with different stimuli in the environment increase the specificity of the responses within these areas. Behaviour is thought to be the outcome of changes in activity over several regions, rather than being predetermined by the actions of one or a cluster of genetic factors. As this is another domain-general framework, it is assumed that the development of communication and the social brain as a whole follows the same dynamic and complex pathways.

There are several assumptions underlying the IS framework that are markedly different from those of the maturational and experience accounts. The assumptions are categorised based on the specialisation or interactive parts of the theory. Predictions concerning the specialisation element suggest that: increased tuning towards a stimulus will change and become more selective over time, from broad responses to many different stimuli to a more selective response pattern; a specialised region will respond less to non-preferred stimuli; changes in specialisation will be associated with the degree of localisation of that response in the cortex; and plasticity of a region will be determined by the degree of specialisation that already occurred, so that a region that is not specialised following damage will be able to develop the functionality of a different region, while fully specialised regions will be less plastic in response to damage and functionality may not be restored.

The interactive component of the framework predicts that: neural change is not likely to be present in just one region, as networks will adjust to optimise overall function; activation of regions will become more fine-tuned to given stimuli or task processing as specialisation extends from specific regions to networks; and the specialisation process will be impacted by the environment across different functional networks. Additionally, specialisation of a single region occurs within the context of interactions with other regions.

The IS framework is distinct in the way it accounts for developmental change, with the predictions allowing to formulate testable hypotheses when evaluating functional imaging studies. Indeed, the framework has been used to explain the development of many infant and child abilities, including face perception (Aylward et al., 2005; Golarai et al., 2007; Joseph, Gathers, & Bhatt, 2011), social cognition (Battista et al., 2018; Lloyd-Fox et al., 2009; Mosconi et al., 2005), word learning (Brown et al., 2005; Schlaggar et al., 2002) and the emergence of executive control (Gaillard et al., 2000; Luna et al., 2001).

1.2.3.1 Evidence for/against Interactive Specialisation.

The IS framework argues that different aspects of the social brain, including face recognition and communication emerge as networks and become increasingly specialised to respective stimulus categories through activity-dependent processes. The processes are facilitated by interactions between the primitive brain areas, cortical areas, and the environment. These assumptions have been used to explain the reported inconsistencies in face recognition skills, e.g. gradual increases in face expertise due to experience (de Haan, Johnson, Maurer, & Perrett, 2001; Libertus & Needham, 2011; Nelson & Ludemann, 1989) and tracking of face-like arrangements a few minutes after birth (Goren et al., 1975; Morton & Johnson, 1991), which have been previously used to argue opposing sides in the nature vs. nurture debate.

Inconsistencies in face recognition research can be explained by applying the IS framework, as it recognises the importance of both intrinsic and extrinsic factors (Johnson, 2011). Specifically, there are changes in the degree of specialisation and localisation of face-processing regions during development. This has been supported by fMRI studies that show an increasingly fine-tuned face network with age (Aylward et al., 2005; Golarai et al., 2007), including the hemispheric lateralisation of responses to faces towards the right hemisphere for children aged 5–8 and 9–11 years (Aylward et al., 2005). Additionally, ERP responses to faces were found to become more specialised with age (i.e. increased amplitude and localisation of response, de Haan, Pascalis, & Johnson, 2002). The evidence therefore suggests that while there are biases to face processing in neonates, they are shaped by experience; and the two act together to produce adult-like levels of expertise and the corresponding localised responses in cortical regions.

The IS framework can further be applied to the emergence of communication abilities and auditory processing as a whole (Johnson, 2011; Scott & Johnsrude, 2003). In typical

development, language experience begins in the womb (DeCasper & Fifer, 1980) and subsequent specialisation towards the native language is driven by the input of sounds from the infants' environment (Scott, Pascalis, & Nelson, 2007; Vouloumanos, Hauser, Werker, & Martin, 2010). There are several behaviours observed in typical language acquisition that can be explained by the assumptions of IS, including perceptual narrowing and audiovisual integration (which are addressed in Chapter 3).

The IS framework further questions the notion of a left hemisphere bias towards language processing by arguing that there are no pre-specified regions of the brain that cannot adapt their function within a certain developmental timeframe. For example, it is argued that simple architecture may exist in the left hemisphere that makes language processing easier in that region and explains why this region is consistently associated with language processing in typically developing individuals, but that language can also exist outside of the constraints of the commonly accepted structures of the 'language network'.

Findings from functional imaging studies further supported the IS framework by mapping the reorganisation of language areas following injury. Some have reported that focal left hemisphere injury can be compensated by activation in the analogous regions of the right hemisphere (Guzzetta et al., 2008), while others reported activation around the focal site of a lesion in the left hemisphere being adapted to language processing (Liégeois et al., 2004; Liégeois, Connelly, Baldeweg, & Vargha-Khadem, 2008). Following stroke in children, bilateral cortical activation as well as increased activation in the frontal cortex has been reported vs. localised activation reported in neurotypical children during silent verb generation (Tillema et al., 2008).

Due to small sample sizes of the studies outlined above, it is difficult to establish individual factors that may predict cortical reorganisation patterns. However, the case evidence is consistent with the IS framework as it suggests that interactions within the brain are able to

support functions such as language following injury to the left hemisphere (see Chapter 1.4.1). Similarly, the left hemisphere can take on other functions in the absence of language (e.g. in Deaf individuals) and Neville and Bavelier (2002) reported that without receiving auditory input from the environment, inter-sensory competition from visual stimuli takes over the cortical regions commonly associated with language areas.

There are some challenges to the IS framework that have be to be addressed. As recognised by Johnson (2011), findings that have been used by supporters of IS may also be explained by the maturational or experience accounts of development. This applies to the finding that language onset occurs around 18 months of age, once the brain reaches a specific level of myelinated white matter and the region is considered 'mature' (Pujol et al., 2006). The framework does not explain why specific brain responses to language have been reported in brain regions that are considered immature from as early as a few months of life (Dehaene-Lambertz et al., 2002), as well as the increasingly advanced auditory discrimination skills across the first year (Blasi et al., 2011; Cheng et al., 2015; Rivera-Gaxiola et al., 2005). The IS framework brings together the opposing arguments of nature and nurture and highlights that development is a more complex dynamic process that is not readily explained through the influence of a single underlying mechanism.

Additional questions arise from evaluating functional imaging methods themselves, specifically whether activity in infant imaging studies is masked by noise or artefacts. This is argued by Köster (2016), who questioned the reported effects due to the possible negative impact of microsaccades on data quality. One commentary suggested that the change from diffused to localised responses in the brain may be due to the number of errors and difference in response times between children and adults (Brown, Petersen, & Schlaggar, 2006). Evidence for the protracted development of different brain regions has been provided by fMRI, NIRS and EEG studies, however, which all use different methods and processing techniques.

Convergent results across several methodological designs have high levels of reliability and are unlikely to only reflect artefacts.

1.2.3.2 Interactive Specialisation: Typical vs. atypical development.

The IS framework provides a comprehensive view of the emergence of developmental disorders. It parallels the views of the neuroconstructivism approach (Mareschal et al., 2007; Westermann et al., 2006) as well as Gottlieb's work on probabilistic epigenesis (Gottlieb, 2002, 2007; Figure 1.1), which highlighted the importance of bidirectional interaction between the individual and the environment. These theories question the traditional view that developmental and genetic disorders are innately specified and exist in single modules and suggest that a single deficit is unlikely to exist in an otherwise intact system. Both IS and neuroconstructivism frameworks suggest that early atypicalities in the development of a region/signalling pathway have downstream effects on the subsequent development of neighbouring cortical structures, which creates domain-general deficits across the whole brain.

Based on these theories, individuals with neurodevelopmental disorders such as ASD and ADHD do not demonstrate deficits specific only to 'social' and 'attention' abilities respectively, but instead show a wide range of impairments across different modalities. The argument is supported by findings of difficulties in sensory processing (Donkers et al., 2015; Glod, Riby, Honey, & Rodgers, 2016) in ASD as well as motor coordination difficulties reported in infants and children with neurodevelopmental and genetic conditions (Karmiloff-Smith, 2013; Rietman et al., 2017). Presence of these domain-independent difficulties can further explain the high co-morbidity between developmental and mental health conditions (Simonoff et al., 2008; van Steensel et al., 2013).

Lastly, the IS framework argues that sampling from the environment may be different in individuals with neurodevelopmental conditions, e.g. the lack of social engagement in

infants with an elevated likelihood of ASD may prompt less engagement from the caregivers. In turn, reduced caregiver input would result in reduced experience and poorer development of communication skills in childhood. Fear of danger/injury might also mean that caregivers limit exploration behaviours, and the infant receives less experience interacting with their environment (Karmiloff-Smith, 2009).

Another important aspect of the IS framework, is that it does not consider atypical developmental trajectories to be purely based on deficits and argues there are many abilities that fall within the typical or even superior range in children and adults with ASD. Rejection of the deficit model has been widely recognised in the literature on visual search and attention tasks (Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009; Keehn, Brenner, Palmer, Lincoln, & Müller, 2008; Milne, Dunn, Freeth, & Rosas-Martinez, 2013). It has been found that superior visual search in infants predicted later ASD outcomes, and was not modulated by attentional engagement (Cheung et al., 2018).

As mentioned previously, a functional imaging study by Pierce and colleagues (2001) reported that individuals with ASD are able to process social stimuli through unique brain circuitry, although this is yet to be replicated using a larger sample. Superior abilities in speech discrimination in adults with ASD relative to neurotypical controls were associated with better receptive language skills, and suggested that this may be an important mechanism in ensuring better language outcomes (Heaton et al., 2008). Others found responses to language stimuli beyond the language regions of the left hemisphere, specifically in the right and right medial frontal regions (Dawson et al., 1986; Redcay & Courchesne, 2008). In this way, ‘atypical’ lateralisation of speech processing in ASD is indicative of an adaptive pathway and alternative processing routes must be considered as an explanation for the ‘deficits’ observed relative to the neurotypical population.

Based on the evidence discussed above, it can be argued that the IS framework offers the most complete theoretical perspective as to what is likely to be happening during early functional changes in the brain and will therefore be considered in the construction of the hypotheses for the set of experiments discussed in this thesis.

1.3 Functional Postnatal Brain Development

Next, I considered the known functional changes that occur in the brain after birth and how these may relate to the established theories of brain development. This was necessary to understand the underlying mechanisms that may facilitate the subsequent onset of a number of social and language skills. Human brain development is exceedingly complex and involves interactions between intracellular signalling and the release of signalling molecules that transfer messages between neural cells and surface receptors. This is heavily influenced by genetic, epigenetic and environmental factors.

The anatomical changes within the brain have been characterised in both rodents and humans (Andersen, 2003; Semple et al., 2013). The morphological development of the brain does not achieve a fully mature state until late childhood/early adolescence, which highlights the amount of time in which genes, structures and the environment can impact brain development. Cortical thickness in different regions develops in a rapid manner that is different across different brain regions (Liu, Nie, Tarokh, Guo, & Wong, 2008; Sowell et al., 2004), which is consistent with the predictions of the IS framework. It should be noted that cortical folding, which begins prenatally is not a mere reflection of the passive unfolding of the genetic code and is instead guided by interactions between the brain and environment, including sex, obstetric history and socioeconomic factors, which have all been observed to have an effect on overall cortical thickness and surface area (Jha et al., 2019). Indeed, the growth and expansion of cortical networks is a key predictor of high-level functional development (Nie et al., 2014).

Next, functional development is considered in more detail. Emergence early structures and activity of neurotransmitters associated with the adult language network are considered in order to lay the foundation to the hypotheses and analytic techniques used in the experimental chapters of this work.

1.3.1 Functional changes.

Due to a recent surge in the improvement of brain imaging technologies, several methods can now be used to measure specific brain functions that were not previously measurable using structural and behavioural methods. These include EEG, NIRS, fMRI and MRS, results from which will be discussed throughout the course of this thesis. There are two common ways of measuring brain activity: steady state (while the infants are asleep or the children are looking at the centre of a screen) and task-related state (which involves passive processing of visual/auditory/touch stimuli in infant participants or simple attention/choice paradigms in older children and adults).

Sleep data in infants has shown the emergence of functional resting state networks, with the first networks evident from 26 weeks prenatal age, where fine-tuning and increased specialisation of responses are observed (Collin & van den Heuvel, 2013; Vértes & Bullmore, 2015). Additionally, it was found that different networks emerge at different points in time (Hoff, Van den Heuvel, Benders, Kersbergen, & De Vries, 2013), with higher-order processes emerging much later in development. While it has been reported that there is activity in all the functional networks associated with the adult brain by term (Doria et al., 2010), they are still relatively immature by the time the infant is born and have a somewhat hierarchical nature in their development (Fransson et al., 2007; Gao et al., 2015; Raichle & Snyder, 2007; Smyser & Neil, 2015; Smyser, Snyder, & Neil, 2011).

Additionally, there are many early functional connections (within and between cortical areas) that emerge as a result of the combination of innately specified mechanisms and sensory-driven neural input (Tau & Peterson, 2010). These connections begin forming during gestation in preparation for the establishment of resting-state networks, which allow better communication between different brain regions over time. Emerging resting-state networks have been recorded using various neuroimaging techniques, including EEG, fMRI and diffusion tensor imaging (DTI; a variant of MRI based on tissue water diffusion rate used in white matter research).

Resting state EEG activity reflects development within the anatomical structures as well as increases in synchronous activity between distal brain regions over time (Niedermeyer, 2005; Vanhatalo & Kaila, 2006). As mentioned above, fMRI studies have reported region-specific activations, although these were relatively immature compared to the adult brain (Heep et al., 2009; Neil et al., 2006). A DTI study further reported differences between term and preterm infants, specifically in the pattern of white and grey matter as well as specific functional pathways (Mukherjee et al., 2002). The increase in connectivity with age demonstrated the strengthening of the relationship between structure and function over time, which is somewhat similar to the changes reported in adolescence using the same technique (Asato et al., 2010; Brouwer et al., 2012).

1.3.2 Neurotransmitter activity in early development.

Another important functional change that occurs during early brain development concerns neurotransmitters and neuromodulators, which are chemicals involved in the propagation of information signalling in the brain. I consider these separately to the main changes in functional development due to the importance of these mechanisms in the emergence of dynamic brain systems, as evidenced by animal/human models of atypical brain specialisation.

The signalling molecules can be classified into intrinsic transmitters that originate within the cortex (e.g. GABA and glutamate) and extrinsic transmitters that are generated outside of the cortex (e.g. norepinephrine, dopamine and serotonin). For the purposes of the present work, I focus on intrinsic transmitters, which are classified according to whether they have an excitatory or an inhibitory function[5].

Glutamate is the main excitatory neurotransmitter, whereby an increase in signalling directly enhances the excitatory tone in the brain. Glutamatergic inotropic receptors NMDA, AMPA and kainite are involved in all rudimentary stages of neurodevelopment as well as synaptic plasticity, a neural mechanism implicated in learning throughout life (Uzunova et al., 2014). Glutamate acts as a trafficking molecule for guiding axons to their designated regions and alterations in normal function can manifest as major cognitive impairments.

In contrast, gamma-aminobutyric acid (GABA) is the most prevalent inhibitory neurotransmitter in an adult brain, making up 10–25% of the total number of cortical neurons depending on the cortical region. It is vital for maintaining temporal precision and integrity of neural firing. In mice, it was found that an induced blockage of GABAergic interneurons resulted in the elevation of glutamate and a hyper-excitable state in the brain (Wehr & Zador, 2003). It has also been linked to human behaviour using MRS, with a negative association found between levels of GABA in the sensorimotor cortex and tactile discrimination performance in adults (Puts et al., 2011, 2017), as well as correlations between an increase in GABA in motor regions and short-term motor learning (Boy et al., 2010; Stagg et al., 2011b).

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[5] Reviews of early functional development within extrinsic neurotransmitter systems are available (de Graaf-Peters & Hadders-Algra, 2006; Herlenius & Lagercrantz, 2001, 2004).

Markedly, GABA signalling is excitatory during development and the functional switch due to the ionic plasticity of Cl^- and $HCO3^-$ ion concentrations in the postsynaptic neurons is now considered an indicator of brain maturation (Ben-Ari, 2002; Rivera, Voipio, & Kaila, 2005). This has been widely accepted in animal studies, where two switches have been reported: a short-term switch that occurs briefly at the point of birth (Tyzio et al., 2014)[6] and a second, permanent 'GABA switch' that has been recorded between birth and the first week after delivery (Ben-Ari, 2014; Valeeva, Valiullina, & Khazipov, 2013). Although there is evidence of this switch in basic organisms through to more complex mammals (see Ben-Ari, Gaiarsa, Tyzio, & Khazipov, 2007 for a review), the timing of the switch in humans is unknown and is estimated to occur following neuron maturation within the first year of life.

There is evidence from animal models that suggested that GABAergic neurons regulate the output of pyramidal cells, which is critical for the emergence of oscillatory activity across different frequency bands (Hájos et al., 2004; Tamás et al., 2000; Whittington et al., 1995; Ylinen et al., 1995). This is particularly important relative to the research questions set out in this thesis, as oscillatory activity has been attributed to many aspects of cognition (Fuchs et al., 2007).

Excitatory glutamate and inhibitory GABA signalling work in equilibrium, stimulating the growth of and toxicity in neurons, respectively. During development, glutamatergic and GABAergic progenitor cells follow different paths to reach their destination and are both excitatory, which is necessary to ensure maximal neuronal growth and synaptic formation (Yehezkel Ben-Ari, 2002; Sultan, Brown, & Shi, 2013). A functional excitation/inhibition (E/I)

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[6] GABA briefly switches from excitatory to inhibitory shortly before birth. This has been found to reduce the likelihood of anoxic episodes (brief stoppage of the heart due to excess vagus nerve activity) during delivery.

balance in adulthood is necessary for regulation of cognition, emotion and behaviour (Luján et al., 2005). Slight alterations within this balance in the brain have been attributed to significant impairments in functional specialisation of the cortex, including links to aberrant sensory processing development in ASD and genetic disorders (Lee, Lee, & Kim, 2016; Rubenstein & Merzenich, 2003; Yizhar et al., 2011) (see Chapter sections 1.5.2 and 1.6.1 for further discussion of E/I signalling dysregulation and its implication in neurodevelopmental disorders).

Importantly, the reliability of methods used to measure the E/I balance in the brain is currently limited by poor spatial resolution and variability in methods, as well as large effects of motion (Ajram et al., 2019; Stagg et al., 2011a). A large majority of studies look at resting state concentrations of neurotransmitters, where the relationship with cognition and behaviour is unclear. This may also capture signals from GABA-like metabolites, which interfere with the estimation of already low GABA concentration levels in the brain. Recent attempts to address this have not yet been successful (Edden et al., 2016). This also appears to be the case for glutamate, as one of the most commonly used processing sequences in MRS does not differentiate between glutamate and glutamine (Stagg et al., 2011a).

It should be noted that some advances have been made in addressing limitations in spectroscopy measurements (Schmidt-Wilcke et al., 2018; Stanley & Raz, 2018), replication is needed to improve the reliability of these analytic protocols. Above all, MRS is an expensive technique and not easily accessible for large-scale developmental studies, with only a handful reported to date (Cady et al., 1983; Kwon et al., 2014; Spencer et al., 2014).

1.3.3 Putative marker of neurotransmitter activity in infants.

One of the ways to measure early changes in the brain is through oscillatory activity (1) during rest or (2) passive processing of stimuli over developmental time. The activity has been

measured through different frequency bands within EEG and MEG signal directly at the scalp's surface.

Gamma activation is thought to reflect the orchestrated stability between populations of excitatory and inhibitory neurons (Buzsáki & Wang, 2012). As such, observing the strength and change in activation of gamma power may offer a suitable alternative for the empirical study of neurotransmitter activity in the brain of individuals with a high likelihood of ASD (see E/I theory by Rubenstein & Merzenich, 2003 in Chapter 1.6.1). The links between gamma activity and neurotransmitter function is supported by several animal studies. Glutamatergic activity at N-methyl-D-aspartate (NMDA) receptors was found to contribute to the generation of oscillations in the gamma (*y*-band) range (30–80 Hz; Carlén et al., 2012) and blockage of NMDA receptors resulted in an absence of gamma-band activation. A further link was made by Balz and colleagues (2016), who reported a strong three-way association between GABA concentration, gamma-band oscillations and individual ability to perceive a sound-induced flash illusion. GABA concentration was positively related to the power of gamma-band oscillations, which led the authors to speculate that there is a causal link between these metrics.

In the typically developing human brain, there is evidence to suggest that the distribution of oscillatory frequencies changes during the first 2 years of life and this has been attributed to the maturation of cortical regions and changes in synaptic activity (Tierney et al., 2012). One of the advantages of observing gamma power is that it is done via EEG and can therefore be used on awake infants with minimal distress relative to other measurements such as fMRI or MRS.

Time-frequency methods of EEG signal processing have also shown higher power in detecting differences relative to standard ERP techniques, based on a direct comparison in an infant auditory processing study (Isler et al., 2012). The following sections consider the specific timeline of development within the communication networks in the brain in typical

development, the differences in neurotransmitter function in developmental and genetic conditions and the possible changes in oscillatory activity.

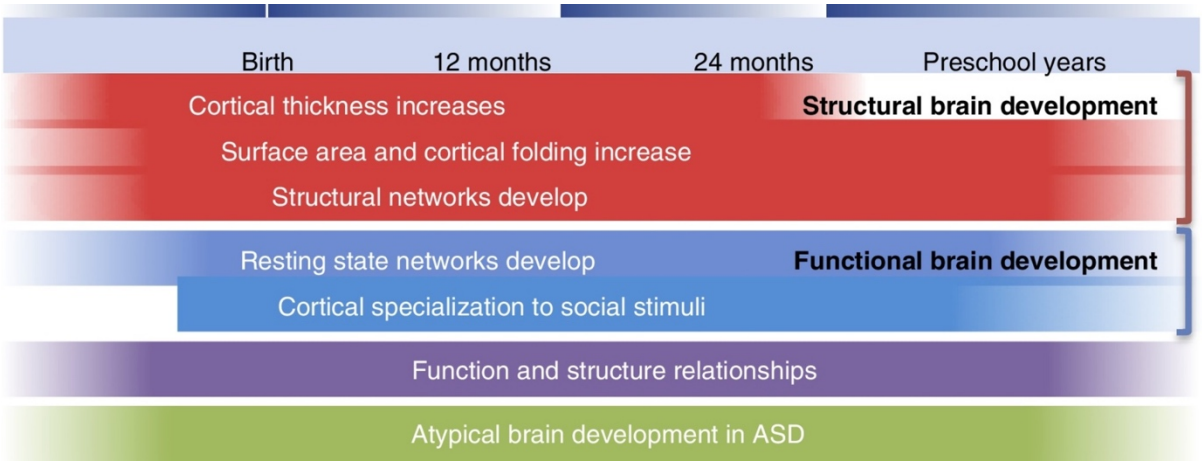

Figure 1.2 Developmental timeline over the first years of life which considers aspects of structural, functional as well as atypical development. Reprinted from graphic abstract by Haartsen, Jones & Johnson (2016).

1.4 Development of Communication Brain Networks

Next, the development of networks associated with social communication was assessed in more detail. By considering early developmental milestones, I aimed to understand how the brain constructs preconditions of learning verbal and non-verbal social communicative behaviours.

From birth, infants display early communicative behaviours in the absence of spoken language. They achieve this through a multitude of prelinguistic behaviours, including orientation to faces and their caregiver's voice and joint attention to external objects (Charman et al., 2000; Reddy, 2016; Reilly et al., 2006). Researchers have argued that these early parent-child interactions are necessary to facilitate infant learning as parents and caregivers play a large role in providing infants with experience of the sounds and gestures of their native linguistic environment. Indeed, commonly observed communicative behaviours such as cooing and babbling are thought to be learned through mimicry (Cruttenden, 1970; Kuhl & Meltzoff,

1996; Sweeney Sheila, 1973). Early face-to-face experiences are also believed to be essential to facilitate the production of words as well as turn taking and subsequent word learning.

One of the most commonly recognised and studied aspects of human communication is the mastery of language that occurs during the first years of life. The 'end state' of language acquisition is associated with the full maturation of a set of structures in the cortex, including Broca's area, Wernicke's area, the angular gyrus and the insular cortex. These regions work together from the initial perception of speech within the environment to categorisation and processing of information into words and word sequences to obtain context and meaning of the linguistic input.

It is also known that there are many structural and functional changes that happen during development to prepare the brain to reach expert levels of comprehension and production of language. Processing of complex speech sounds has been reported in near-term foetuses at around 38 weeks gestational age through bone conduction between the amniotic fluid to the foetal skull and the inner ear (Granier-Deferre et al., 2011). It was further reported that there were both brain and heart rate changes in response to the mother's voice (Jardri et al., 2012; Kisilevsky & Hains, 2011).

After birth, functional imaging evidence has allowed us to visualise an early network for processing language in neonates, with basic connections established between different areas of the brain that develop into adult-like networks with strong inter-region connectivity around school age (Brauer et al., 2013). This observation provided a neuropsychological basis to examine prelinguistic communicative behaviour and existence of this basic connectivity network may explain infant 'preference' for their native language as early as two days after birth (Moon et al., 1993), which previously led researchers to believe that language is special in terms of developmental processes and sets human infants apart from other mammalian species. The observation of dynamic changes in functional connectivity from infancy to early

childhood supports the IS framework. It argues that increased experience with the social environment and exposure to the native language not only aids in the maturation of these regions, but also strengthens the connectivity between different regions of the language network.

1.4.1 Is language hemisphere specific?

As highlighted by evidence for the maturational framework discussed above, the left hemisphere has been recognised as a central hub for language processing in the child and adult brain (Friederici, 2009; Szaflarski et al., 2006). The increased accuracy and popularity of brain imaging techniques over the last three decades have supported the notion of left hemisphere bias in the processing of speech stimuli in infancy (Blasi et al., 2015; Dehaene-Lambertz & Baillet, 1998; Minagawa-Kawai et al., 2011; Shultz et al., 2014). Indeed, there is a gradual increase in localisation of responses to faces/voice that has led researchers to conclude that functional specialisation towards processing of social information occurs within the first year of life.

Other studies have found, however, that while responses were higher in the left hemisphere, there was no significant differentiation between speech and tonal stimuli (Dehaene-Lambertz, 2000; Dehaene-Lambertz et al., 2002). Taking the IS view, it can be argued that an innate left hemisphere bias may exist as a sensory mechanism that facilitates processing of any sound and eventually adapts to the most common sound heard in the infant's environment: speech. The 'language' pathway can also be altered or adapted in cases of atypical developmental trajectories (Goldmann & Golby, 2005; Knaus et al., 2008; Li et al., 2014). As such, the left hemisphere may be more active during perception of certain sounds, while plasticity and specialisation towards communication can occur outside of these regional boundaries.

The particular importance of the left hemisphere as a region responsible for language development was evaluated through several early studies on infant lesions and focal brain injuries (Oglio et al., 1994; Thal et al., 1991). It was found that while there was a lot of variability in communication and language abilities, infants with damage to the left hemisphere showed poorer rates of vocabulary production (Thal et al., 1991). Additionally, damage to the right vs. the left hemisphere resulted in overall better language ability with deficits in word comprehension and gestures (Vicari et al., 2000). These arguments have been used to support the maturational framework, i.e. the left hemisphere processes speech and damage to the associated areas means that language alone is impaired.

Although the sample sizes of such studies are relatively small and replication is very difficult, detailed qualitative data can be obtained from these unique samples. It should be noted that communication is not fully absent in the case reports and language skills are highly variable and present within a typical range, albeit within the low-average range (Goodglass, 1993; Muller et al., 1999). Based on what is known about the nature of infant brains, focal damage is unlikely to be contained to a specific region and instead may drive a different developmental trajectory impacting a wide range of skills and abilities.

Other factors affecting brain injury outcome include age of acquisition, cause of injury and size of injury and developmental time (Bates et al., 1999). Additionally, there is evidence for recovery and neuro-reorganisation as performance reports on behavioural and cognitive tasks showed typical scores across different scales in a population of children with focal brain injuries whose injuries occurred *after* the critical window for the development of these skills is thought to be closed (Stiles, Reilly, Paul, & Moses, 2005). Findings of left hemisphere bias have also been questioned by the results of other investigations that have found both right hemisphere dominance and unilateral responses to phonemic contrasts (Arimitsu et al., 2011; Homae et al., 2006) and localisation towards the left hemisphere after 13 months of age

(Minagawa-Kawai et al., 2007). These results suggest a more protracted development of left-hemisphere specialisation towards language.

Lastly, a recent study of children with left perinatal arterial ischemic stroke found evidence of structural and functional reorganisation of connectivity within the right hemisphere at 4 years of age, which was in turn associated with better language outcomes (François et al., 2019). Taken together, the literature suggests that while the left hemisphere is more likely to functionally specialise towards language processing in typical development, other regions including the right hemisphere can effectively 'take over' in cases of early focal brain injury or atypical processing as an outcome of neurodevelopmental disorders.

1.4.2 Language processing outside of the left hemisphere.

Human voices are processed in the superior temporal sulcus (STS), with higher activation reported in the right compared to the left hemisphere in adult fMRI studies (Belin et al., 2002; Fecteau et al., 2004). This has been associated with the voice sensitive response (VSR) in EEG (a differential waveform between voice and non-voice stimuli near the latency of the P3 component), which has been reported in adults and typically developing children aged between 4 and 5 years (Bidet-Caulet et al., 2017; Rogier et al., 2010; Samira et al., 2010).

Based on the predictions of the IS framework, it could be argued that the human voice is one of the most commonly heard stimuli and therefore a region of the brain becomes increasingly specialised with experience. It has been reported that foetuses and neonates show significant changes in heart rate in response to different voices and show recognition of the voices of their parents (Kisilevsky et al., 2003; Ockleford et al., 1988). Adult-like responses in the temporal voice areas were reported in 1-month-olds, although the activation patterns undergo significant developmental changes (Grossmann et al., 2010; Patterson & Werker, 2003; Purhonen et al., 2004).

Blasi and colleagues (2011) examined the origins of neural specialisation to voice by looking at BOLD activation in 3–7-month-old infants in response to adult non-speech vocalisations. Researchers found that voice responses in the right anterior STS occurred from 3 months relative to other sounds, with differentiation of sad but not happy voices. It was argued suggests protracted change in development based on experience with voices (i.e. infants interact with more people and hear more voices as they age, which shapes the activity within the specialised region). Increased voice processing is highly important for the development of communication, as infants begin matching the auditory sources to their visual displays, i.e. matching voices to faces, which is necessary for imitation and articulation of native phonemes and words.

1.4.3 Critical periods for acquisition of communication and language.

Bates and colleagues (1992) identified a peak transition in both neural and behavioural development around 8–9 months of age associated with the formation of long-range connections in the frontal cortex and adult-like levels of metabolic activity. Within the first 6 months of life, infants are thought to learn the prosody and rhythms of the language within their environment, which is followed by increasing narrowing towards their native language until the end of the first year (Elsabbagh et al., 2013; Maurer & Werker, 2014; Ortiz-Mantilla, Hämäläinen, Realpe-Bonilla, & Benasich, 2016).

Simultaneously, it has been reported that infants change the way in which they coordinate their attention through neural adaptation to different facial features, which allows information to be captured and learned (Bates, 1999). Specifically, infants are thought to pay attention to the mouth rather than the eyes at around 8–10 months of age, which allows them to learn mouth shapes and precedes the onset of the first spoken word (Barenholtz, Mavica, & Lewkowicz, 2016; Boisferon, Tift, Minar, & Lewkowicz, 2017; Lewkowicz & Hansen-Tift, 2012; see Chapter 3 Task 3). The findings suggested that there are critical periods in brain

development during which functional connections are formed and the emergence of specific skills including various aspects of communication can be accommodated. This has been supported by evidence from brain growth studies, which suggest that an increase in the percentage of brain growth corresponds to developmental milestones in children (Sakai, 2005; Figure 1.3).

In the field of language development, many studies have investigated the efficacy of cochlear implants[7] and it has been found that cochlear implantation carried out after 12 months of age results in poorer language growth relative to infants whose operations were carried out at around 6–12 months, with the latter able to match their typically developing peers (Dettman et al., 2007; Miyamoto et al., 2003). Researchers have attributed the differences in the success rates of the surgery to the advantage of earlier experience with spoken language. Findings from the EEG tasks used in these studies were subsequently used to produce an objective hearing screening measure, which allowed the NIH to lower the minimum age of the surgery to 12 months in 1993 (Tomblin et al., 2005).

It should be noted, however, that other studies have reported good recovery rates following cochlear implant surgery up to 1.5 years (Hammes et al., 2002; Nicholas & Geers, 2007; Sharma et al., 2004). The critical period theory can be questioned further as it fails to take into account the individual variability outside of the age factors reported within these populations (for example, one study reported that the age of implantation accounted for 14.6% of the variance in the improvement in expressive language; Tomblin et al., 2005) or why there

[7] A surgical alternative to hearing aids that is used to facilitate speech development in infants and young children with suboptimal hearing thresholds, e.g. bilateral sensorineural hearing loss (Svirsky et al., 2000).

are large individual differences in typically developing populations in the first year of life who do not experience impairment in communication and language.

Similar to the variability in the outcomes of brain injury cases, it appears that factors including the type of technology used, length of use and educational setting also affect the success of the surgery in supporting communication and language development in infants and young children with severe to profound hearing loss (Connor et al., 2000; Geers et al., 2003; Osberger et al., 2002; Tobey et al., 2003).

Another limitation associated with the idea of critical periods in development is that they often rely on cross-sectional designs and passive listening paradigms, both of which fail to capture the dynamics of early development. When measuring specific abilities in different populations across different arbitrary points during development, many early development studies failed to control for the large external and individual differences by assuming that chronological age was the only factor at play in the emergence of these skills (Karmiloff-Smith, 2010, 2018). This is a key observation that became the focus of the present thesis, including assessment of the validity of the behavioural markers of specialisation in typical development (e.g. perceptual narrowing and audiovisual integration) as well as their utility in predicting outcomes. These issues are further addressed Chapter 3 of this work.

Overall, it can be argued that while there is evidence for hemisphere dominance towards language processing in early infancy, this does not represent innate specificity of the human brain towards language acquisition. This is largely supported by the ability of language processing structures to develop outside of the expected ‘network’, with recent evidence showing associations between high levels of expressive and receptive language skills and the degree of functional reorganisation of the dorsal pathway (François et al., 2019). It is also known that basic communication networks exist from birth and are therefore useful for studying the predictors of later language outcomes. Although there is a wide range of studies

describing the emergence of social communication abilities in infancy, there are gaps in the understanding of individual differences across typical development. Thus, the ability to predict outcomes across a range of different developmental trajectories in infants with familial or monogenic likelihood of developmental disorders remains poor.

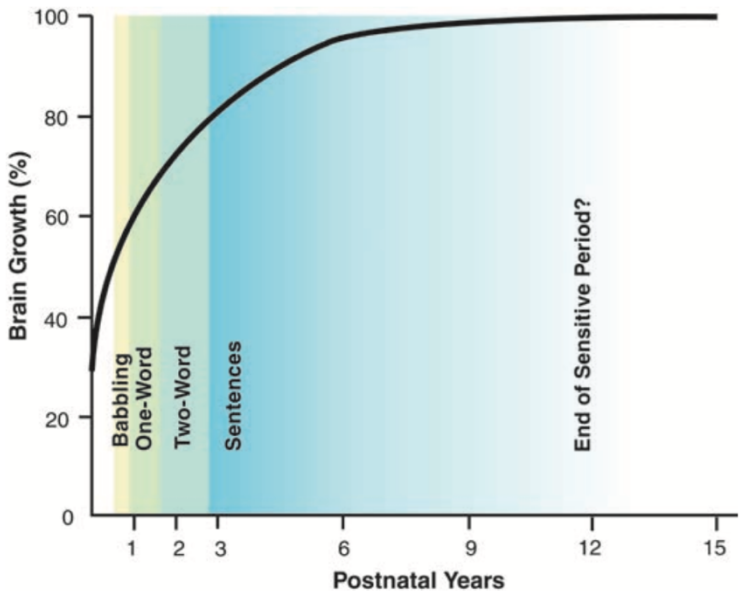

Figure 1.3 Trajectory of brain growth and first language acquisition. Human brain growth is presented as a function of age with 100% corresponding to mean adult brain volume against approximate linguistic milestones in children. Adapted from Sakai and colleagues.

1.5 The Case of 'Atypical' Specialisation: Exploring Familial Pathways to ASD

Another way to study early development and identify key markers of specialisation in the brain is by looking at the differences in early processes between typical and 'atypical' development, i.e. when expected developmental processes do not occur or occur across different regions or time frames. As highlighted in the discussion of the theoretical frameworks above, research into ASD symptomatology has often focused on isolating selectively impaired

cortical regions that could give rise to the phenotype. Examples of this include deficits in ToM (Baron-Cohen et al., 1985; Happé, 1995), function of the cerebellum (Courchesne et al., 1988) and the frontal cortex (Pennington & Welsh, 1995; Shalom, 2009).

It should be noted that studies of atypical brain development are often driven by the assumptions of the adult neuropsychology model, which suggests that impairments in isolated brain regions have specific effects on behaviour. As a result, the investigations focus on differences in function or specific impairments in selected regions, rather than looking at the outcomes of interactions across the whole brain. The adult neuropsychology model does not hold when considering early brain development as distinct patterns of behaviour are a likely outcome of widespread and variable changes across individuals (South et al., 2008). Additionally, there is evidence to suggest more generalised impairments in children with ASD beyond social communication difficulties, including reduced gross motor skills and non-social auditory processing (Glod et al., 2016; Miller et al., 2014).

In the following section, the experience-dependent processes within the social communication network are explored in infants who go on to develop ASD. Findings from some phenotypic studies suggested that difficulties in social communication are an adaptive outcome based on perturbations in the cortical system during early development. It is then considered how these different information processing strategies may influence the emergence of ASD-specific symptomatology, including sensory processing difficulties (sensory-level) and delays in language acquisition (higher-level skill) in this population. Lastly, prospective longitudinal infant sibling designs are put forward as the optimal way of gathering data and consider the current findings as well as the advantages and limitations of this method.

1.5.1 Communication as a 'selective' impairment?

There is evidence to suggest that specialisation of social communication skills is impaired in infants later diagnosed with ASD. As previously highlighted, difficulties in social communication make up half of the dyad of the current diagnostic criteria of ASD (American Psychiatric Association, 2013), while reduced/absent language is widely reported in individuals with the diagnosis. It was thought by many that ASD is a condition that selectively affects communication and the social brain (Baron-Cohen et al., 1985; Scholl & Leslie, 1999), however, more recent studies report intact language processing in ASD in the presence of an added visual component (Kamio & Toichi, 2000; Moseley et al., 2014; Sahyoun et al., 2009).

There have been reports of additional brain regions recruited following presentation of language stimuli in individuals with ASD. Specifically, parietal and occipital areas were found to be activated together with the language cortex, a pattern that is not observed in typically developing individuals (Kana & Wadsworth, 2012; Kunda & Goel, 2011; Samson et al., 2012; Shen et al., 2012). Recent advances in neuroimaging techniques and more in-depth longitudinal assessments have therefore altered the original reductionist view to argue in favour of different developmental trajectories and neurodiversity. To date, there are gaps in the understanding of the cortical basis of communication and language dysfunction in ASD as well as the failure to gain 'expertise' in social processing.

One of the strongest findings in the field is that in contrast to typically developing individuals, there is a lack or reversal of hemispheric specialisation within language networks in ASD (see Herringshaw, Ammons, DeRamus, & Kana, 2016 for a meta-analysis) This has been observed on structural and functional levels through several MRI (Gage et al., 2009; Herbert et al., 2002; Kana & Wadsworth, 2012) and EEG studies (O'Reilly et al., 2017; Yoshimura et al., 2013). It has further been suggested that atypical hemispheric specialisation is region dependent, rather than the whole brain being 'right' or 'left'-lateralised (Nielsen et

al., 2013). For example, there has been evidence for the absent or reduced mapping of visual cortex responses in children and adults with ASD, which suggested more widespread atypicalities in functional specialisation (Frey et al., 2013; Vlamings, Stauder, van Son, & Mottron, 2005). Jochaut and colleagues (2015), on the other hand, reported reduced connectivity between auditory and other language-related cortical brain areas and suggested that there may be dysregulation in the mapping of information between sensory input and higher-order representations within the brain.

Atypical lateralisation is thought to occur early in development, as several studies have reported higher right hemisphere activation during a speech perception task in toddlers and infants with an elevated likelihood of ASD (Eyler, Pierce, & Courchesne, 2012; Seery, Vogel-Farley, Tager-Flusberg, & Nelson, 2013). Right hemisphere lateralisation of speech processing at 12 months further predicted ASD outcome at 3 years of age, suggesting that this may be an early diagnostic marker (Finch et al., 2017). 'Atypical' lateralisation, however, has been seen in neurotypical children and adults that are left-handed or ambidextrous, and children and adolescents with ASD who did show left hemisphere lateralisation were more likely to be right handed (Groen et al., 2008; Knaus et al., 2008; Szaflarski et al., 2006). It may not be specific to ASD, as atypical lateralisation of brain function in processing of language stimuli in children and adults were noted in ADHD, Schizophrenia and Dyslexia (Edgar et al., 2006; Hale et al., 2006; Xu et al., 2015). Examining lateralisation in the present sample may provide important information for this debate, although there is limited evidence as of yet to form robust hypotheses for the ASD sample.

More recent studies using fNIRS have revealed atypical voice processing in ASD. In the typical brain, there are several regions associated with voice recognition and vocal emotion processing, including the STS, the amygdala and premotor cortical regions (Blasi et al., 2015). This has been supported by evidence of functional activation of these areas in infancy

(Dehaene-Lambertz et al., 2002; Lloyd-Fox et al., 2013). An fMRI study reported that there is gradual specialisation towards voice processing throughout the first year of life that resembles adult responses to human voices and negative emotions (Blasi et al., 2011). On the other hand, neural responses to voice may differ in individuals with a family history of ASD. One study found that infants with a familial risk of ASD did not show selectivity to voice stimuli across different language regions and showed a reverse pattern of hemispheric activation at around 5 months of age (Blasi et al., 2015).

Findings outlined above can be used to inform why atypical EEG responses have been reported during social versus non-social tasks in infants with later ASD (Jones, Gliga, Bedford, Charman, & Johnson, 2014). Specifically, there is enhanced processing of non-social sounds, i.e. higher attention towards environmental noise in ASD (Bonnel et al., 2003; Klin, 1991; Whitehouse & Bishop, 2008). In terms of everyday learning, higher brain activation to environmental noise would impair development of expertise within social interaction and communication.

It can be argued that the expected markers of early communication and the language network may function atypically in ASD, which is an argument embedded in the context of atypical specialisation of the whole brain. Taking the RDoC approach highlighted above (Cuthbert & Insel, 2013) may be useful when characterising the phenotype, especially as the prelinguistic markers of communication are largely unidentified in both typical and atypical development.

ASD is a pervasive developmental condition that affects many aspects of everyday life and one of its symptoms is sensory aberrations, which are present in up to 90% individuals with ASD (Glod et al., 2016; Marco et al., 2011).This may be the result of atypical neural signalling, where all incoming stimuli are not perceived or processed in an adaptive way, resulting in a dysfunctional cortical system. It must be acknowledged that communication

difficulties may be a manifestation of deficits across all sensory processing systems, although they do present an appealing therapeutic target in infancy and early childhood, particularly due to the importance of communication abilities in reaching school readiness and when navigating the social world.

Based on the research above, specific research questions have been identified.

1) *Can we identify predictors of atypical development in childhood? How early can we detect atypical speech and language processing in infants and children?*
2) *Are these atypicalities persistent over time?*
3) *How can we use familial designs to investigate different levels of impairment?*

The following sections aim to address these questions and propose future avenues for research.

1.5.2 Infant sibling design.

More recently, studying infants with a family history of ASD has proven to be a useful avenue for investigating early predictors of atypical development. The incidence of ASD in the general population is around 1–3% and ADHD between 5 and 8.3% (Danielson et al., 2017; Hire et al., 2018; Russell et al., 2014), which means that very large sample sizes would be required from the general population to capture a sufficient number of infants who are on a spectrum of neurodiversity.

Alternatively, an infant sibling design can be used (Peter Szatmari et al., 2016), in which infants are recruited based on their family history. Infants with an older sibling or first-degree relative with a diagnosis of a neurodevelopmental condition can be regarded as having an 'elevated likelihood' of receiving the diagnosis themselves as the incidence rates increase to 25% for ASD and 26–45% for ADHD (Hidalgo-López et al., 2019; Ozonoff et al., 2011). Using this strategy has meant that a much higher percentage of infants who will go on to receive

a diagnosis of ASD can be recruited. A control group of infants who do not have any family history of genetic or neurodevelopmental conditions is also included.

Another valuable aspect of infant research is that it allows us to examine differences within the early physiology that precede symptom onset on a behavioural level, thereby providing more effective pre-emptive intervention strategies (Webb et al., 2013). This has been widely used in the literature across several research groups (Gardener et al., 2011; Hazlett et al., 2017; Webb et al., 2014), as well as within the BASIS project (Shephard et al., 2017; www.basisnetwork.org/), data from which is included in Chapters 5 and 6.

Prospective longitudinal studies of infants with older siblings with ASD have yielded significant insights into the early differences within this population (Jones, Gliga, Bedford, Charman, & Johnson, 2014). In the first year of life, behavioural differences in infants with later ASD are difficult to detect and appear robust in sensory and motor functioning only (Clifford et al., 2013; Estes et al., 2015). For example, 6-month-old infants with later ASD are more likely to show poor head control (Flanagan et al., 2012) and infants at familial risk show poor postural control (Nickel et al., 2013) and have limited reaching and grasping skills (Libertus et al., 2014). In contrast, social communication appears relatively typical in the first 6 months (Estes et al., 2015; Ozonoff et al., 2010). However, neurocognitive measures reveal subtle atypicalities in social engagement (Jones et al., 2016) and response to eye gaze (Elsabbagh et al., 2012) and a declining interest in looking towards the eyes over time (Jones & Klin, 2013).

There is also evidence for early differences in communication behaviour in individuals who are rated by clinicians as showing clinical levels of ASD symptomatology. By the end of the first year, differences have been reported in a range of ASD-related behavioural phenotypes, including poorer language and communication skills (Estes et al., 2015), reduced joint attention (Macari et al., 2012), diminishing social interest (Ozonoff et al., 2010) and the

emergence of unusual interests in objects (Ozonoff et al., 2008). Measures like the Autism Observational Scale for Infants have also shown reasonable sensitivity to ASD outcome at this time (Gammer et al., 2015; Zwaigenbaum et al., 2005), although a stable diagnosis is not made until the second or third year of life (Ozonoff et al., 2015). Therefore, it appears that clear delays in ASD-relevant domains emerge over the first year of life but may be preceded by alterations in early brain development that affect lower-level sensorimotor systems.

A recent study reported the effects of parent speech on later language outcomes using an infant sibling design. Swanson and colleagues (2019) found that in all infants, irrespective of family history or later diagnosis of ASD, increased early experience with social interaction had a strong effect on language skills at 2 years of age. Parental education effects were mediated by the richness of the auditory environment provided to the child. In addition, it was found that typically developing infants experienced an increase in conversational turns between 9 and 15 months of age, although the same pattern was not observed in ASD. These mediating effects indicate that early interventions to increase the quantity and quality of early parent-child interactions may have a protective effect on language and school readiness in a child with elevated familial likelihood of developmental conditions.

There are some limitations to the infant sibling design, including the length of time it requires to collect the data as the infants age. Additionally, developmental outcomes are not known until the child is 2–3 years of age, which delays the ability to group individuals based on developmental outcome rather than likelihood. There is evidence that individuals with first-degree relatives with the condition show elevated levels of ASD traits, however, and can be classified as the Broad Autism Phenotype (BAP; Sucksmith, Roth, & Hoekstra, 2011), with several infant studies reporting differences in early processing between infants with and without a family history of ASD (Isler et al., 2012; Jin et al., 2015; Kaur et al., 2015).

By reporting these early differences in infants who do not go on to present with any neurodevelopmental conditions, it is possible to identify potential protective factors within the environment that may alleviate the more severe symptoms. Partial data presented in Chapter 4 and 6 of this work emerged from an ongoing study of infants with an elevated likelihood of ASD/ADHD or with a genetic condition called NF1. The outcome data for the sample is not yet available.

1.6 Molecular Basis of Specialisation

The following section considers the underlying biological mechanisms behind typical and atypical brain specialisation. Firstly, molecular pathways that may impact the process of specialisation are described, due to their importance for the design and efficacy of individualised treatments. Maintenance of neurotransmitter activity in the young brain is thought to be critical for cortical function and it has been suggested that this balance is disrupted in ASD (see Chapter 1.6.1). Due to large heterogeneity within idiopathic manifestations of the condition, it can be difficult to understand the underlying aetiology. This has been addressed through single-gene and animal models of ASD, which are described below.

It should be noted that there is evidence for both increases and decreases in neural excitability in ASD and that alterations within neurotransmitter balance are not specific to the condition, but are observed in many neurodevelopmental, psychiatric and genetic disorders. The latter point is particularly important to consider in order to understand the common and divergent pathways to ASD and how molecular paths to the ASD phenotype may be shared across different conditions (Gandal et al., 2018; Gao & Penzes, 2015).

1.6.1 Excitation/Inhibition imbalance as a mechanism of neurodevelopmental disorders.

Evidence of atypical glutamate and GABA function in early brain development has been used as an explanation for ASD aetiology. Rubenstein and Merzenich (2003) reasoned that an imbalance of excitatory and inhibitory neurotransmitter function reduces signal-to-noise ratio and leads to a hyper-excitable brain network. The proposed Excitation/Inhibition (E/I) balance theory argued that over-reactivity at the neural synapse impairs the basic mechanisms of information processing and learning and as such, adequate communication and language ability cannot develop. This is supported by the finding that 50–70% of children with ASD demonstrate an ongoing spike in their resting state neural activity and poor long-range connectivity (Maximo et al., 2014).

Several MRS studies also reported enhanced glutamatergic (Uzunova et al., 2014) and reduced GABAergic signalling (Hussman, 2001; Pizzarelli & Cherubini, 2011), which has become a prevalent explanation for ASD aetiology. The theory is further supported by the finding that reduced GABAergic activity diminishes inhibitory control in signalling and prevents efficient processing of incoming information (Rippon et al., 2007), as well as evidence from animal models (Coghlan et al., 2012; Lee et al., 2016). It has been argued that GABAergic hypofunction alone could elicit the E/I imbalance by compromising connectivity and increasing cortical noise at baseline.

There are also many studies that argue for the opposite direction of neurotransmitter balance (i.e. decreased levels of glutamic acid enzymes and their mRNAs; Shimmura et al., 2013; Yip, Soghomonian, & Blatt, 2007), as well as findings of inconsistencies in the direction of the E/I balance across brain regions or a complete absence of group differences between ASD and neurotypical populations (Purcell et al., 2001).

The aberrant precision account (Lawson, Rees, & Friston, 2014) has recently been used to place the E/I theory within the wider framework of the disorder. Based on the predictive coding network, the aberrant precision account suggested that ASD symptoms arise from a disturbance in normative sensory processing. Construction of accurate outcome predictions for external events on a cellular level can be explained by transmission of glutamate, GABA and other neuromodulators. NMDA receptors modulate communication between higher and lower-processing areas, thus GABAergic hypofunction may underlie the inability to form prior expectations (Horder et al., 2013; Purcell et al., 2001).

Typically, outcome predictions from higher brain areas are imperative for reducing sensory ambiguity. Individuals with ASD may lack precision of these prior beliefs, which increases uncertainty. Due to the importance of clarifying ambiguity in interactions, a preferential bias emerges for sensory auditory input. Lee and colleagues (2007) further hypothesised that this is achieved through enhanced activation within the visual areas and a reduction in prefrontal cortex activation during decision making in primates. Essentially, the findings suggested that there is an over-reliance on incoming sensory information in ASD. Individuals who are unable to form accurate predictions about the outside world may become isolated, unable to participate in social communication and start to engage in repetitive or self-injurious behaviours (where ambiguity of sensory stimulation is reduced).

The accounts outlined above offer an interesting perspective into how dysfunction in basic auditory mechanisms can affect subsequent development and behaviour. To construct a viable ‘causal chain’ explanation of autism, the effects of dysregulated glutamate-GABA signalling need to be understood. Due to limited availability of technologies to measure neurotransmitter function directly, there is not a sufficient amount of evidence to argue presence of E/I imbalance in infants with later ASD. Looking at brain responses across the first years of life may allow an alternative non-invasive way of identifying these changes and

constructing more accurate representations of the early function of the sensory-level auditory mechanisms that may have downstream effects on the phenotype.

The following sections highlight the current evidence for a neuromodulator dysregulation as the aetiology of ASD, evaluate the contribution of various techniques used within the field and offer possible ways to investigate predictions of these theories using infant-friendly methodologies.

1.6.1.1 Animal models.

Due to the difficulty in measuring E/I balance in human participants, the majority of understanding of its function originates from animal work. There is reasonably high similarity in cortical structure and social behaviours between humans and rodents, which validates the use of animal models in the study of neurological abnormalities in autism. One transgenic mice model (Gandal et al., 2012) found that inhibition of the genes that regulate receptor activity during neurodevelopment resulted in ASD-like symptomology. It was argued that suppression of activity at NMDA receptors increased extracellular levels of glutamate. As a result, the mice presented with reduced social interaction and communication, engaged in repetitive behaviours and demonstrated restricted interests relative to 'neurotypical' mice. Manipulation of genes that regulate glutamate transmission in mice has been associated with the onset of abnormal social behaviour and increased anxiety (Choudhury, Lahiri, & Rajamma, 2012; Karlsson et al., 2009) and reversal of ASD-phenotypes following correction of the E/I balance in animal models suggests that this biological mechanism is an important target when designing therapeutic interventions (Lee et al., 2016).

A review of several ASD mice models concurred that induced GABAergic hypofunction resulted in cortical hyper-excitability (Lee et al., 2016; Limon & Miledi, 2011). It was found that genes that regulate GABA signalling levels directly affect the shift in E/I

balance as innervations of rat hippocampi manifested in glutamate and GABAergic receptor dysfunction (Ferraguti, 2017; Limon et al., 2011). Summary of the findings from several rat models by Choudhury and colleagues (2012) further suggested that alteration within normative GABAergic function leads to a disrupted E/I equilibrium and a subsequent ASD behavioural phenotype. The authors further hypothesised that alterations in analogous receptors within the human hippocampus would disrupt the typical synchronisation of cortical activity, although methodological difficulties mean that these studies have not yet been adapted to human studies.

Importantly, animal models highlight the role of epigenetic factors on GABAergic expression. At birth, knockout mice lacking in the MECP2 protein implicated in GABA signalling presented no distinct functional or anatomical abnormalities (Chao et al., 2010). Within the first weeks of life, however, stereotyped movements, compulsive grooming and hyper-excitability within the brain were observed in the sample. Similarly, epigenetic regulation of GABAergic activity has been put forward as an aetiology of various neurological conditions and associated with respective behavioural outcomes, supplemented by evidence from both human and rodent studies (Keverne, Pfaff, & Tabansky, 2015; Shrestha & Offer, 2016; Sultan & Day, 2011). The model could be used to explain the gradual onset of behavioural symptoms in children with autism as a result of early developmental aberrations.

More recently, a computational *FmrI* (Fragile X) knockout mouse model revealed that the standard E/I model was too inflexible to account for simultaneous alterations in neurotransmitter firing rates as well as changes in circuit mechanisms across development (C. O'Donnell et al., 2017). Researchers further argued that due to the complexity and multidimensionality of E/I in neurodevelopmental conditions, experimental predictions should be focused on a single circuit or mechanism, which can then be linked to physiology. Irrespective of similarities between vertebrate brains, however, direct conclusions about

transmitter function require longitudinal studies as well as computational models based on data from human participants.

1.6.1.2 Brain tissue analysis.

Brain tissue analysis has provided evidence to support abnormal glutamate-GABA function in adults with ASD. Casanova (2006) and Casanova and colleagues (2002) reported findings from post-mortem samples of brain tissue from individuals with ASD. Computerised imaging program analysis of columnar morphology concluded that within the frontal and temporal lobes, minicolumns[8] were smaller, horizontally dispersed and more abundant relative to samples taken from neurotypical controls. Further investigation using digital micrographs recognised substantial variability between cortical regions: in some areas, neuron density was 23% higher for ASD compared to the comparison group (Casanova, 2006).

Lateral inhibition by GABAergic neurons has been found to modulate organisation of minicolumns within the neocortex (Rubenstein & Merzenich, 2003) and this has been used as evidence that early developmental stages are compromised. Higher column count can be attributed to dysregulation of the synaptogenesis and pruning processes, whereby the disproportionate neuronal growth leads to greater cortical expansion. This is consistent with observations of higher brain volumes in children diagnosed with ASD (Lee & Bigler et al., 2007). Smaller neuronal cell sizes in conjunction with higher distances between them produce an inefficient cortical network.

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[8] Cortical minicolumns are ventral columns that run through the cortical layers II-IV in the brain, containing 80-100 neurons (Casanova et al., 2002; Mountcastle, 1997). They are considered to be a fundamental structural unit of the cortex.

Conversely, ASD symptoms have been associated with a prolonged hyperglutamatergic state in the brain (Fatemi et al., 2008). Post-mortem analysis of the cerebellar tissue of nine individuals with ASD revealed abnormalities within the glutamatergic regulation system in the cerebellum and hippocampus (Purcell et al., 2001). As such, mRNA levels for genes that regulate the glutamate system were higher in samples from individuals with ASD than neurotypical controls. Higher levels of mRNAs were also associated with decreased density of AMPA glutamatergic receptors and excitatory proteins (Na+-dependent glutamate transporters or EEATs), mechanisms typically responsible for long-term potentiation and preventing excitotoxicity in the adult brain. Purcell and colleagues (2001) concluded that the combination of glutamate transporter system abnormalities in the cerebellum was directly associated with pathology in ASD. This study highlights the importance of considering systems beyond GABA function, although the wide age range of samples and missing evaluation of ASD symptoms limits the ability to apply these findings to existent electrophysiological or behavioural evidence.

It should be noted that observations of post-mortem samples are unlikely to fully explain the developmental changes that precede the onset of ASD. Due to maturational processes and the brain plasticity that occurs throughout life, post-mortem analyses may essentially reflect secondary manifestations of autism and the related compensatory strategies. This criticism is reinforced by a comparison of tissue composition between adults with and without ASD *in vivo* (Horder et al., 2013). Researchers did not observe differences in grey or white matter volume and only small deviations were reported between the size of the basal ganglia and the cortex. In addition, causes of death in brain tissue analysis often include hypoxia or traumatic brain injury (Purcell et al., 2001), which means that potential atrophy of the sample material negates the quality and reliability of the proposed conclusions.

1.6.1.3 E/I imbalance in children and adults with ASD.

It has been highlighted above that development of neurotransmitter signalling pathways is central to the emergence of functional brain networks that are able to support higher-order cognitive function. The importance of inhibitory processes has also been supported by the finding of abnormal $GABA_A$ receptor density in the brain tissue of individuals with ASD (Blatt & Fatemi, 2011; Fatemi et al., 2008). In the absence of adequate inhibition, cortical circuit refinement and sensory binding are compromised, both of which correspond to the atypical sensory processing that has been recognised within ASD symptomatology. This section considered present evidence for atypical E/I in individuals with a diagnosis of ASD.

A longitudinal MRS study in children with ASD found region-specific alterations in GABA concentration, including lower GABA in the motor and auditory regions of interest but not the visual system (Gaetz et al., 2014). Although both motor and auditory system deficits are reported in ASD, no significant associations were found with the behavioural measures collected during the study. Notably, the study by Gaetz and colleagues (2014) employed a MEGA-PRESS analytic technique, which has shown some success in differentiating GABA from other, much more prevalent metabolites.

Atypical GABAergic signalling in ASD has been corroborated by evidence from a larger sample MRS investigation with children with and without the condition, which found reduced GABA levels in sensorimotor areas but not in the visual cortex (Puts et al., 2017). Taken together, these findings suggest region-specific reductions in GABA within sensory areas in individuals with ASD, which is supported by EEG and behavioural findings of atypical and sensory responsivity to sounds and failure to habituate to sensory aspects of the environment (Magdalena et al., 2016; Rojas, Maharajh, Teale, & Rogers, 2008; Vivanti et al., 2018).

Taking a more translational approach, one study directly compared glutamate/GABA concentrations in adult humans, rats and mice and found abnormalities in the concentration of these signalling molecules in the striatum and medial prefrontal cortex, structures associated with social reasoning and higher-order decision processes (Horder et al., 2018). A review of the MRS literature looking at the concentration of GABA and glutamate in samples of patients with paediatric disorders found that glutamatergic dysregulation underlies early psychopathology across many developmental conditions, with the strongest evidence in support of glutamatergic dysregulation in ADHD and bipolar disorder (Spencer et al., 2014). On the other hand, dysfunction in GABAergic pathways has been associated more closely with ASD and similar conditions, including Fragile X, Rett syndrome and foetal anticonvulsant syndrome (Coghlan et al., 2012).

At the present time, a consensus on the nature of the E/I imbalance in ASD has not been reached (Brix et al., 2015; Dickinson et al., 2016), largely due to the limitations of the measurement techniques and the differences in analysis pipelines. It is not currently possible to study the E/I balance in the human cortex through non-invasive or infant-friendly neuroimaging methods, which highlights the need for the identification of the translational markers of neurotransmitter activity.

1.6.1.4 Atypical neural oscillations in ASD.

Neural activity at different frequencies has been used as a predictor of cognitive function and as a putative marker of E/I balance in several studies (Orekhova et al., 2007; Port et al., 2017; Rojas et al., 2008). In ASD, there is evidence to suggest atypical activity and divergent trajectories across all frequencies in infants with elevated familial likelihood of ASD relative to neurotypical controls during rest (Tierney et al., 2012).

Evidence to support the association between gamma power, E/I and ASD was put forward by Orekhova and colleagues (2007), who found enhanced gamma power during sustained visual attention in boys with ASD relative to age-matched controls. This was also positively related to the rate of developmental delay. The researchers argued that elevated high frequency oscillations reflected 'pathological' oscillatory activity, which may be generated by atypical GABAergic and/or glutamatergic receptor systems.

Furthermore, enhanced frontal gamma has been put forward as an adaptive mechanism as infants with higher gamma power were observed to have better inhibitory control and attention switching (Benasich, Gou, Choudhury, & Harris, 2008). Tanigawa and colleagues (2018) somewhat supported this view as they observed lower gamma power over language processing networks in adolescents with ASD. There is difficulty in interpreting these results, however, as resting-state data is subject to movement artefacts and may not reflect true gamma activation.

Task-based designs have further suggested that there are atypical auditory responses within the gamma band in children and first-degree relatives of individuals with ASD, which was related to symptom severity (Rojas et al., 2008, 2011). These responses were also observed in the visual (Dickinson et al., 2015; Seymour et al., 2018; Sysoeva et al., 2016) and motor domains (An et al., 2018), leading researchers to suggest that atypical gamma function may be a generalised mechanism that indexes atypical information processing. Additionally, atypical gamma activity has been observed across several developmental and genetic syndromes, including Fragile X (Ethridge et al., 2016; Wang et al., 2017), schizophrenia (McNally & McCarley, 2016) and Williams syndrome (Grice et al., 2001), albeit the direction of the abnormality in Williams syndrome differs to that observed in age-matched adults with idiopathic ASD.

It has also been suggested that interactive acoustic experience at 6 months of age increases discrimination ability within the theta band at 9 months of age (Ortiz-Mantilla et al., 2019), which may be investigated as a potential sensory-level marker for auditory processing difficulties in infants with elevated likelihood of ASD. Further, theta power increases have been reported consistently during auditory discrimination in typically developing infants (Bosseler et al., 2013; Musacchia et al., 2015, 2017), although there are no studies to date that have investigated theta power in infants with later ASD and its associated links with behaviour.

Although there are limitations to frequency and time-frequency methods, which will be discussed throughout the course of this work (Chapters 2, 5 and 6), they offer a way of investigating brain activity in awake individuals with developmental and genetic conditions with relative ease. It should be noted that there is still extensive debate about the E/I imbalance as an underlying aetiology of ASD, and thus the supposed downstream effects on the oscillatory activity of the cortex, due to inconsistency in findings across many ages and methodologies. Therefore, finding an indirect marker of E/I itself will *not* be the focus of the present work, although these underlying mechanisms are important to consider when discussing the wider implications of neurophysiological findings.

The E/I framework has been highly influential in the field, further driving the understanding of the genetic and neural factors underlying ASD and the effects of specific gene factors and pharmacological interventions that target inhibitory function (e.g. arbaclofen trials; Winter, 2019). Many researchers in the field support the need to study cellular and circuit mechanisms as well as generate translational research that will bridge the gap between human and animal studies. This will be addressed in the second part of the thesis, where I considered differences in oscillatory function in ASD and neurotypical development to evaluate the usability of EEG-based markers in predicting symptomology.

1.6.2 Investigating atypical specialisation in single-gene disorders.

Although prospective studies of infants with elevated familial likelihood for ASD have provided us with important insights regarding the early signs of the condition (Jones et al., 2014), they represent a vastly heterogeneous sample with many risk or protective factors that may impact developmental outcome. The unclear aetiology further complicates the interpretation of animal models, which mainly use single-gene knockout approaches and therefore do not address the full polygenic complexity of idiopathic ASD. Any interventions or pharmacological treatment strategies are therefore unable to address the particular neurobiological systems that are affected.

One way in which this can be addressed is by looking at the development of infants with known genetic syndromes characterised by a heightened incidence of ASD as part of the phenotype. This has been identified through animal models for Fragile X, tuberous sclerosis complex (TSC) and NF1. However, these conditions are considerably rare. Identified genetic syndromes only account for a small proportion of cases of ASD and the generalisability of the mechanisms observed in particular disorders therefore remains unclear (Richards et al., 2015). The optimal strategy may be to establish which antecedent biomarkers observed in studies of infants at familial risk are also present in infants with genetic syndromes. In this way, generalised causal paths that are likely to be widely applicable can be identified and can also be more carefully probed at the molecular and neurobiological levels. For the purposes of this work, I focused on NF1 only, due to comparable developmental abnormalities as well as the unique nature of the sample.

1.6.2.1 NF1: Case for atypical specialisation of molecular and behavioural pathways.

Neurofibromatosis Type 1 (NF1) is an autosomal dominant neurocutaneous[9] disorder with a birth incidence of 1:2,700 (Evans et al., 2010). Fifty percent of cases are inherited, while the rest are *de novo* cases due to spontaneous loss-of-function mutation of the NF1 gene (OMIM 613113) located on chromosome 17q11.2. This gene encodes for neurofibromin, a large 2818-amino acid negative RAS GTPase-regulating protein. The locus on chromosome 17 is one of the highest recognised rates of single-gene mutations in the human genome (John, Ruggieri, Ferner, & Upadhyaya, 2000; Reynolds et al., 1992; Uusitalo et al., 2014). Although well known for its cutaneous manifestations (including café-au-lait spots, neurofibromas, Lisch nodules of the iris and abnormalities within the skeleton and the central nervous system), the main challenges reported by parents and children with NF1 in clinical settings are cognitive, social and behavioural difficulties.

In contrast to other monogenic syndromes, NF1 is not complicated by severe intellectual disability. Although seizures may complicate presentation of the disorder, they are reported much less frequently than in other conditions (e.g. 4.2% incidence of epilepsy in NF1 versus 54–85% in TSC and 10–20% in Fragile X) and individuals with NF1 rarely receive anti-seizure mediation (Berry-Kravis, 2002; Chu-Shore et al., 2010; Korf et al., 1993). The overall IQ is in the low average range and specific learning impairments are common (Lehtonen et al., 2015).

There is a high prevalence of ASD in NF1, with up to 25% of the paediatric NF1 population presenting with full ASD and an additional 20% presenting with ASD

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[9] Neurocutaneous disorders/syndromes affect the brain, spinal cord, organs, skin and bones, with tumours growing in these areas throughout the course of life.

symptomology, as well as higher severity of ASD symptoms in cases where NF1 is inherited (Garg et al., 2013; Morris et al., 2016). It should be noted that the incidence of ASD has not been considered a feature of NF1 up until two decades ago (Gillberg & Forsell, 1984; Svend E. Mouridsen et al., 1992). Currently, prevalence rates are contested in the literature as some studies report lower incidence rates in other populations (Eijk et al., 2018; Richards et al., 2015; Williams & Hersh, 1998).

Due to the late recognition of this co-morbidity, many infants with NF1 do not receive a diagnosis of ASD and any behavioural problems are attributed to the genetic condition, which may explain why many children present with significantly lower non-verbal communication abilities than those with ASD without NF1 (Bilder et al., 2016; Green, 2014). Importantly, the phenotypic profile of ASD in NF1 is broadly similar to idiopathic ASD (Garg et al., 2015), with a similar male bias in prevalence of ASD in this condition (Shruti Garg et al., 2016), making insights from NF1 more likely to generalise to the understanding of ASD as a whole. Similar avenues have been pursued in other single-gene disorders, validating the current protocol (Lane et al., 2016; Peters et al., 2004).

1.6.2.2 Excitation/Inhibition balance in NF1.

Theoretical models of ASD argue that ASD symptomology arises due to an E/I imbalance in the brain, which has downstream effects on hyper/hypoexcitation of the cortex and leads to an inability to learn and efficiently process information from the outside environment (Chapter 1.6.1; Rubenstein & Merzenich, 2003; Rubenstein, 2010). NF1 is considered as a suitable single-gene model to test this theory as E/I imbalance is part of the physiological presentation of the disorder due to (1) known alterations of GABA levels in the brain (Costa & Silva, 2002; Violante et al., 2013) and (2) increased incidence of ASD, ADHD and developmental delay (Garg et al., 2013; Hirabaru & Matsuo, 2018; Vogel, Gutmann, & Morris, 2017).

Alterations in GABA activity in animal models have also been associated with deficits in learning and memory (Costa & Silva, 2002; Molosh et al., 2014; Omrani et al., 2015; Shilyansky et al., 2010). An NF1 mouse model that measured neurotransmitter concentration and levels of GABA receptors through MRS observed a disruption in E/I balance that was region specific (Gonçalves et al., 2017), while increased GABA neurotransmission was reported relative to the reduced cortical GABA levels reported in human studies. Another recent study by Maloney and colleagues (2018) found comparable alterations in communitive behaviour between two NF1 mouse models, which led researchers to argue that NF1 mutant mice should be investigated further for both potential causative factors and treatments for ASD. Mouse models are important for understanding human biology due to genetic and physiological similarities between the species. Due to differences between animal and human environmental adaptations, however, there is considerable difficulty translating this research directly onto human participants (Perlman, 2016).

Moreover, several studies of children and adolescents with NF1 reported phenotypic similarities with ASD, including atypicalities in face processing, communication, social interaction and attention relative to the typically developing population (Barton & North, 2004; Fisch et al., 2007; Huijbregts et al., 2010; Thompson et al., 2010). These behavioural symptoms have been attributed to dysregulation within the RAS signalling pathway (Pierpont et al., 2018; Schwetye & Gutmann, 2014), although research is limited in investigating the role of this pathway outside genetic disorders. Additionally, there have been reports looking at atypicalities in basic auditory processing in NF1 (Batista et al., 2014), which corresponds to the idiopathic ASD literature. It can be argued that dysregulation in auditory processing mechanisms may be the overarching factor between familial and genetic paths to ASD, which will be investigated throughout the course of this work.

Due to current gaps in the understanding of early development in this population, this thesis reported findings from the first prospective study with infants with NF1 and looked at developmental trajectories and the contribution of genetic and familial factors towards ASD likelihood.

1.7 Thesis Overview

In this thesis, I explored the developmental paths towards communication abilities in preverbal infants. This was initially addressed by measuring the commonly observed markers of language expertise through eye tracking in typical development (Tasks 1-3, Chapter 3) and evaluating whether these markers are valuable in predicting individual variation in communication and language abilities. Identifying markers of specialisation towards speech and language processing was particularly important in the context of existing literature, which has been largely based on passive viewing/listening paradigms as well as highly manipulated stimuli.

In the second part of this thesis, differences in auditory processing mechanisms in infants with atypical developmental trajectories were investigated using EEG. Responses to repetition and change of vowel sounds were observed longitudinally at 5 and 10 months in infants with typical development as well as NF1 (Chapter 4). Next, basic habituation (Chapter 5) and auditory steady-state paradigms (Chapter 6) were used to assess the basic aspects of auditory cortex function in infants with varying degrees of familial or monogenic likelihood of ASD. Results from EEG experiments were then evaluated based on the previous literature on E/I alterations in atypical neurodevelopment, in order to inform translational models and pharmaceutical interventions in early life.

Based on the current evidence, the main questions that will be addressed by this work are:

1) It is possible to capture early specialisation towards the native language in typically developing infants using novel eye tracking paradigms?

- *Are infant-driven and naturalistic eye tracking experiments equally able to capture specialisation, i.e. increase in perceptual narrowing and increasing 'preference' measured through basic gaze indices and pupil dilation towards the native language stimuli with age (Chapter 3).*
- *Can relationships be established with EEG-based markers of auditory processing and the behavioural phenotype? Specifically, can we find dimensional associations between gaze/pupil dilation metrics, neural habituation and parent/observer reports of infant communication and language abilities in the typically developing sample? (Chapter 4).*

2) Can putative EEG-based markers of auditory cortex specialisation be established and are they predictive of later language outcomes in toddlerhood?

- *What are the age-related changes in neural ERP and oscillatory brain responses to auditory stimuli; and can I establish relationships with parent and observer report of early child development? (Chapters 4-6).*
- *Is it possible to differentiate cortical responses in the gamma and theta power bands in response to basic auditory stimuli depending on individual likelihood of neurodevelopmental conditions such as Autism Spectrum Disorder (Chapters 5-6) or ADHD (Chapter 6)?*

3) And finally, what are the differences in early communication in infants with the rare genetic disorder Neurofibromatosis Type 1?

- *Are infants with a diagnosis of NF1 showing age-related differences in neural speech processing relative to neurotypical infants?*
- *Are there group differences between infants with NF1 and those with idiopathic ASD/ADHD? Are established EEG measures of specialisation including habituation*

and deviance detection sensitive in capturing similarities/differences between these populations? (Chapters 4 and 6).

Chapter 2. General Methods

The following chapter describes the several methods used to investigate specialization towards speech and language processing in the infant brain, which will be investigated throughout this thesis. I will elaborate on the different ways in which experimental results from these techniques may be analysed, as well as consider strengths and limitations of their application to the study of early brain development.

For the longitudinal study of typically developing infants, several behavioural and physiological methods were used to answer the questions set out within the main aims of the project. Both eye tracking and EEG have been utilized to provide comprehensive view of experience-dependent specialization and deliver converging evidence on potential mechanisms involved. Specifically, physiological measures can help understand the possible underlying neural mechanisms of perceptual and/or cognitive processes. This was supplemented by observer and parent-report measures of infant abilities, temperament and language, which are more representative of behaviour in an everyday context.

Additionally, this thesis explored the emergence of auditory specialization in the context of atypical development (due to familial or genetic history) primarily focusing on physiological data from EEG recordings and its links to parent-report measures of infant behaviour. Observing these populations further allowed understanding of mechanisms underlying experience-dependent specialisation in a unique sample. It will further consider if questionnaire-based measures are sensitive to the individual phenotype, and whether these associations are related to the chosen EEG-based indices of brain specialisation.

It must be noted that there are both advantages and disadvantages endemic to infant physiological and behavioural studies. Physiological measures of brain activity, such as EEG, are sensitive to movement, blinks and shifts, and require high numbers of trials. This is so that

an average of the data can be taken, which is less sensitive to artefacts present in individual trials. This is not the case for behavioural measures, which allow some movement and gaps within the data. They further require fewer trials than is used for EEG. Nonetheless, behavioural techniques may be less sensitive to the underlying cognitive processes (i.e. behavioural techniques rely on reaction time that is measured in seconds vs. EEG which allows responses from different brain regions to be tracked with millisecond precision). This further supports the reasoning behind using a combination of these techniques to measure the relationship between brain and behaviour. Extensive discussion of the strengths and challenges of using these methods is presented in Chapter 2.1.

The first technique will be the behavioural measures, specifically gaze-contingent paradigm (ET Task 1, Chapter 3) as well as gaze orienting behaviour (ET Task 2 and 3, Chapter 3). These will be outlined briefly as markers of social cognition and language in infancy. This will be followed by a general introduction of the EEG, ERP and time-frequency techniques used for the study of auditory specialization (EEG Task 1, Chapter 4), responses to repetition and auditory change (EEG Task 2, Chapter 5) as well as frequency modulation (EEG Task 3, Chapter 6) in infants in the first years of life. In addition, the advantages and disadvantages of using EEG to measure brain activity are discussed in regards to research with infant populations, and specifically infants with genetic disorders and those with elevated likelihood of neurodevelopmental conditions due to family history. This is particularly important, as there are several practical concerns beyond data quality that have to be taken into account when working with special populations. Finally, I described the analysis of EEG signal, within both time (ERP) and time-frequency domains (amplitude, power, ITC), which can provide a more sensitive measure of cortical responses beyond conventional ERP-paradigms.

2.1 Behavioural Methods

2.1.1 Visual behavioural techniques.

Looking is one of the first behaviours that emerges in infancy, where the gaze is attracted selectively to certain objects or events. Studies of neonates and very young infants show that they are attracted by movement, and especially faces and face-like stimuli (Johnson, et al. 1991). Looking behaviours and eye movements (saccades) are long-established measures of infant discrimination ability (Fantz, 1958, 1963) and are often used to understand early cognitive development (Eckstein et al., 2017). Eye tracking techniques have a broad range of application, including studies of allocation of attention and interest (Franchak et al., 2015; Taylor & Herbert, 2012), understanding and recall (Lai et al., 2013; Taylor & Herbert, 2012), social interaction (Ahtola et al., 2014; Gredebäck & Melinder, 2010; Pfeiffer et al., 2013), language acquisition (Bergelson & Swingley, 2012; Kovács & Mehler, 2009) as well as atypical development (Jones & Klin, 2013; Merin, Young, Ozonoff, & Rogers, 2007; Young et al., 2009).

Although measurements of infant gaze through experimenter observation were pioneered almost 90 years ago (McGinnis, 1930) and refined over 50 years ago through photographic techniques (Salapatek & Kessen, 1966), recent automatization of gaze coding has propelled the methodology forward allowing quicker and more reliable data collection procedures as well as electronic analysis of each video frame (for review of the history of eye tracking techniques see Aslin & McMurray, 2010). The technique most commonly used is corneal reflection (CR), which uses a light source to illuminate the eye and causes visible reflections that are picked up by a camera. This image is then reconstructed as a vector of an angle between the light source of the cornea and the pupil as well as other geometric aspects of the reflection, which can then be used to calculate gaze direction (Aslin & McMurray, 2010; Gredebäck, Johnson, & Hofsten, 2009). Using advanced imaging-processing algorithms, this

technique provides high spatial and temporal accuracy of the gaze. Eye tracking does not require a baseline level of verbal or cognitive ability, and thus can be used with preverbal children and infants. And, perhaps most importantly, it can be used in longitudinal paradigms to understand change in a given ability or behaviour.

Gaze behaviour is believed to tap into active cognitive processes, i.e. looking direction towards a particular object is driven by underlying neural mechanisms, which regulate detection, identification and discrimination of the presented visual stimulus (Aslin, 2012). Different looking behaviours are attributed to specific mechanisms: i.e. longer looking times are associated with preference, faster reaction times associated with learning/age-related changes in stimulus processing, when the infant looks away from a stimulus it is termed avoidance, and when infants look longer towards an event, which is impossible in the view of an adult, it is termed violation of expectancy. This has further been studied through combined eye tracking and neurophysiological recordings, where the authors suggest that attention shifting and gaze behaviour can be linked to individual variability in brain activation patterns, supposedly due to the links between cortical maturation and gaze (Kulke et al., 2015; Yuval-Greenberg et al., 2008).

Availability and ease of the new technique has introduced some theoretical complications, namely the over-interpretation of eye tracking data as a direct index of neurological function. One of the biggest challenges of using visual preference paradigms is that while infants are able to discriminate change in visual or auditory domains, they may not always show overt preference through looking times (Aslin, 2012). Further, direction of gaze is not perfectly correlated with visual information uptake (e.g. blank stares or covert shifts of attention), which should be taken into account when designing the task and the analysis pipeline.

Recent methodological advances have allowed more in-depth analysis of the infant gaze which may provide key insights into experience-dependent specialization over the first years of life. These are gaze-contingent paradigms, orienting paradigms as well as analysis of pupil responses. The present thesis features data from both gaze-contingent and scanning paradigms that was used to explore age-related indices of specialisation, specifically in relation to the native language in typically developing infants. This will form the initial cognitive indices of language specialisation (Level 1), which will then be supplemented by neurophysiological markers of sensory language processing (Level 2), as well as parent and observer reports (Level 3). The links between neural markers and behaviour are further discussed in Chapter 2.6.

2.1.1.1 Orienting paradigms.

Eye tracking studies of infant populations, through both automated and manual coding methods, largely involve orienting or 'visual preference' paradigms, which have been used to look at discrimination of objects (Franklin, Pilling, & Davies, 2005; Horowitz et al., 1972), faces (Johnson et al., 1991; Oakes & Ellis, 2011), and language-based stimuli (Maye et al., 2007; Shukla et al., 2011; Werker & Yeung, 2005). It was found that infants as young as 4 months are able to orient towards a stimulus, disengage from a stimulus and produce 'anticipatory' looks (Johnson, Posner, & Rothbart, 1991). In order to minimise problems associated with infant looks (the possibility of them looking equally at different visual stimuli), researchers in these studies present several pairs of competing stimuli, from which a systematic preference pattern is established (Colombo & Mitchell, 2014). However, the passive nature of these paradigms means that results have to be interpreted with caution. This is addressed in Chapter sections 2.1.4 and 2.1.5, where a combination of gaze-contingent paradigms and pupil dilation is used to infer preference.

In the visual domain, orienting paradigms have been used to look at audiovisual speech perception and learning. A pioneering study by Kuhl and Meltzoff in 1982 showed that infants looked longer at the side of the screen where the video matched the vowels spoken at 5 months of age. It was suggested that matching of audio and visual speech cues was present in the first year of life (Kuhl & Meltzoff, 1982). This was further replicated with different vowel contrasts, different genders of speaker (Patterson & Werker, 2002), different languages (Kubicek et al., 2014), and in infants as young as two months of age (Kuhl & Meltzoff, 1998). It was also found that social influences, i.e. exposure to more than one language and maternal speech style were related to the individual ability to discriminate phonemes and later vocabulary size (Altvater-Mackensen & Grossmann, 2015; Kubicek et al., 2014; Kuhl et al., 1992). These findings suggest that audiovisual speech perception is a robust phenomenon in preverbal children, and the emergence of this ability is driven by naturalistic experience.

Task 2 Chapter 3 features a similar preferential looking task, to explore individual variability in audiovisual matching, including effects of age and language experience (Bedford et al., 2016). This is a classic passive viewing task, where infants' looking times are measured based on their orientation towards the video where the syllable repeated matches the congruent video animation or still image of the speaker's mouth (see Chapter 3.7 for task details). Previous investigations showed robust increases in audiovisual matching responses up until the age of one, which suggested that the paradigm would be appropriate to the study of specialisation.

Orienting paradigms can also be used to look at infants' exploratory behaviour of the presented stimulus or scene, and is particularly useful when looking at developmental changes in exploration patterns (Frank et al., 2011). Passive viewing of social videos revealed age-related changes in viewing based on social motivation and complexity of the action. In a large sample of infants between 3 and 30 months of age, Frank and colleagues (2001) reported that

younger infants looked more at the eyes and older children at the mouth when faces only were presented. Further, when complex scenes were shown, younger infants looked more at faces, while preference for looking at hands increased with age. Researchers concluded that there is protracted development in attentional control towards more complex aspects of the visual scene. Some of the limitations of this research however is that it is a cross-sectional design, and individual levels of language and social experience were not taken into consideration.

Developmental change in exploration patterns has been instrumental in informing researchers on pre-verbal language learning behaviours. A cross-sectional study of infants between 4 and 12 months of age found that attention was shifted away from the eyes and to the mouth between 4 and 8 months to both native and non-native speech, and this was followed by a shift back to the eyes at 12 months only for native speech (Lewkowicz & Hansen-Tift, 2012). The initial attentional shift to the mouth is thought to facilitate syllable production, as this is the region where infants are able to gain highly salient information that specifies the native speech forms which they are learning. Once this task is mastered, infants move their gaze back to the eye information, demonstrating both the presence of perceptual expertise and narrowing (Lewkowicz & Ghazanfar, 2006a, 2006b; Maurer & Werker, 2014; Pons et al.,2009). As infants have had less experience with the non-native language, they do not show the second attentional shift. This is supported by findings of delayed attentional shifts from simultaneous bilinguals (Albareda-Castellot et al., 2011; Astheimer et al., 2016; Pons et al., 2015) as well as infants with later ASD symptomatology (Jones, Carr, & Klin, 2008; Jones & Klin, 2013). Task 3 Chapter 3 featured results from passive viewing of English and Dutch nursery rhymes. Specifically, it explored developmental change in looking towards the eyes and mouth of the speaker and how these changes are mediated by individual levels of language experience.

2.1.1.2 Gaze-contingent paradigms.

One way to address the limitations introduced by orienting/looking time paradigms prevalent in infant perception literature, is to introduce an interactive element. Through gaze-contingent paradigms, infants are able to associate a specific look direction with a stimulus, which can then be used more objectively to interpret underlying cognitive processes. This has been used in several studies (Pfeiffer et al., 2013; Vernetti et al., 2018; Wang et al., 2012), where infants and toddlers were able to drive their looking towards the location of a 'preferred' or a rewarding stimulus.

It has been argued that active paradigms provide more in depth information on the neural mechanisms of social behaviours as they are able to engage the bidirectional nature of interaction between the infant and their environment. This method has been mostly used to study joint attention mechanisms. It was found that this process requires a combination of cognitive mechanisms to enable engagement in joint attention as well as a motivation to engage which emerges within the first year of life (Hepach, Vaish, & Tomasello, 2012; Tomasello et al., 2005). It is therefore a more robust measure of infant cognitive processing, although it has been shown that some task effects do not hold up when the task requirements depend on an active response from the infant or toddler (Keen, 2003) .

2.1.1.3 Pupil dilation.

A further method contributing to the study of affective processing is pupillometry (Hepach & Westermann, 2016; Laeng et al., 2012). The pupil is a small opening in each eye which dilates in response to luminance levels and also to novel/interesting events. Physiologically induced changes in pupil size are thought to reflect the activity of the autonomous nervous system (Bradley et al., 2008), and have shown sensitivity to emotional stimuli and attentional/cognitively demanding tasks in adults. It has been shown that changes in pupil diameter are associated with attentional switching, working memory and task difficulty

(for review see Pfeiffer et al., 2013). Because of this, changes in pupil diameter are used in infancy and child research to understand physical and social cognition.

There are several advantages of using pupillometry data to capture infant attention and early cognitive processing over and above basic gaze indices such as looking or reaction time. Firstly, pupil dilation data is continuous over time rather than cumulative, which allows for analysis of the time course of visual processing (Aslin, 2012; Hepach & Westermann, 2016). Secondly, the pupillometry response does not diminish over trials, and can be detected if the participant becomes tired and is therefore highly appropriate for use in infant research (Sirois & Jackson, 2012). Thirdly, the mechanisms behind pupil dilation are analogous between infants and adults (i.e. activation of a subcortical structure locus coeruleous) and is therefore an unbiased marker of activity of the nervous system (Laeng et al., 2012). The majority of studies of pupil diameter, however, use static gaze/orienting paradigms, which ignore the dynamic nature of social interactions. Therefore, a combination of active gaze and pupil diameter are important sources of information in the study of social cognition and early development of the social brain (Aslin, 2012).

Based on this evidence, a language preference task was created (Task 1; Chapter 3) to look at active seeking of language input in preverbal infants (Kolesnik et al., *in preparatioin*). In addition to analysing the video stimulus chosen, looking time, reaction time and pupil diameter data are also described. The three tasks outlined above form the indices which was used to predict neural and behavioural markers of specialisation.

2.2 Electro-physiological Methods

Electroencephalography (EEG) has been used in several of the studies reported in this thesis to investigate infant brain responses to auditory stimuli. The following section describes the rationale for using this technique with the infant population as well as the equipment and

procedures used. The equipment and methods vary from those used with adults. Note that several different signal processing techniques are discussed, namely ERPs and time-frequency approaches, as well as inter-trial phase coherence, which are distinct in their interpretation and application.

2.2.1 Why use EEG?

Over the recent decades, EEG has been used to conduct non-invasive recordings of brain activity in neonates, infants, and other non-verbal populations, which are not possible through behavioural paradigms. EEG does not intrinsically require motor or verbal responses to be produced and allows some movement flexibility. It is also not limited to a specific age-range, thereby permitting one technique to be used longitudinally, which is essential when studying the developing brain. Excellent temporal resolution of this technique is also highly suited to studying experience-dependent changes in brain activity (i.e. specialization), as it allows to visualize these processes with millisecond precision. In infants and children, this has been successfully utilized to look at habituation (McNamara et al., 1999; Turk-Browne et al., 2008), change detection (Friederici et al., 2002; Musacchia et al., 2015), working (Bell, 2012) and recognition memory (de Haan, 2007; Reynolds & Richards, 2005), as well as atypical development (Guiraud et al., 2011; Levin, Varcin, O'Leary, Tager-Flusberg, & Nelson, 2017; Nelson & McCleery, 2008; Orekhova et al., 2014).

It should be noted that limited verbal and motor abilities of infants has influenced the design of the experiment relative to adult tasks, including decreased number of trials, reduced complexity of the stimulus and the number of independent variables (de Haan, 2013) This has led to the emergence of 'resting state' task designs, where infants are exposed to videos of spinning toys or nursery rhymes (Jones, Venema, Lowy, Earl, & Webb, 2015), or passive listening paradigms where the sounds are played in the background while the infant engages in silent play with the experimenter (Guiraud et al., 2011). The setup has also meant that

combining behavioural and physiological methods is not always possible. Although the EEG may inform us on how the brain functions during certain behaviours, it also increases complexity and length of testing time (de Haan, 2013).

There are several other disadvantages to the EEG method which should be emphasised. The spatial resolution of this technique is poor, making it difficult to isolate the neural source that generates the activity recorded at the scalp. Furthermore, the EEG signal is subject to artefacts, which are electrical signals not of neural origin. Biological artefacts include eye saccades and blinks. The signal may also reflect heart rate and myogenic activity (EMG) generated through movement. This is a particular challenge with infant research, as it is difficult to keep them still throughout the testing session. In order to minimize the effect of movement, the infant is typically sat in their parent's lap with their torso held still.

Another significant limitation of the EEG method is the small amplitude of the neural signal relative to task-irrelevant noise (background EEG and artefacts described above). Signal-to-noise ratio can be improved by increasing the number of trials for each condition, as averaging allows for the noise to be cancelled out. This has been successfully adapted in adults, where more than several hundred trials are recorded in each condition. However, this is a challenge with infant populations, where there is only a limited time window in which the data can be recorded. One way in which this problem has been approached is by random allocation of infants to different conditions, which are then compared. This is not a very practical solution, as large individual differences between participants means that many confounding variables are introduced (de Haan, 2007). It is more likely that improving the design and procedure of the experiment will provide an acceptable signal-to-noise-ratio, particularly as infant brain signals tend to be higher in amplitude to that of an adult (DeBoer et al., 2013), somewhat reducing the number of trials required. Potentials recorded at scalp level are likely to be generated by multiple cortical and subcortical generators, which are spread across a large area

(Pizzagalli, 2007). Using high density electrode nets, classified as 64 electrodes and above, helps alleviate this problem, and may be used in source localization (Reynolds & Richards, 2009).

There are age-related changes in EEG and morphology and latency of ERP components (de Haan, 2013; Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002) and EEG rhythms (Tierney et al., 2012), which are independent from changes expected based on the experimental paradigm. However, it is extremely difficult to isolate the underlying processes behind that change due to a combination of dynamic developmental changes (e.g. changes in myelination, synaptic density, neurotransmitter signalling; Haartsen, Jones, & Johnson, 2016) and physiological maturational processes (e.g. skull thickness, total brain volume, hemispheric growth; Knickmeyer et al., 2008)).

Perhaps the biggest limitation in using the EEG method is understanding the nature of the recorded signal, and in particular the function of the ERP component (Luck, 2005). Some believe that neural activity resultant from synchronous firing of populations of neurons is an epiphenomenon, and does not correspond to active cognitive processes (Osherson et al., 1998), although the possibility of this can be minimised by introducing different experimental conditions. Nonetheless, it is difficult to isolate a particular component and measure it independently. Using 'peaks' (maximum or minimum voltage) within the waveform is not an appropriate identifier of components. Several steps have to be taken when designing the experiment and formulating the hypothesis to avoid ambiguities in interpreting the ERP components within the waveform, which are discussed below. The same principle was applied to time-frequency analyses, due to limited understanding of the relationship between neural oscillations and power at different frequency bands. Recognising these limitations in regards to own research and existent literature is necessary to avoid making erroneous conclusions (i.e. about the source of the signal, or the relationship between the signal and behaviour).

Lastly, one of the most appealing features of the EEG signal is that it is multidimensional. The majority of literature using this method often describe the signal in the two-dimensional space (i.e. voltage change over time and electrode location), yet it can actually be conceptualized in four dimensions: time, space (electrode location), frequency and power (i.e. the strength of activity at a given frequency), and phase (timing of the activity) (Cohen, 2014). This provides a unique opportunity to examine theories of specialization based on principles rooted in both psychology and neurophysiology in a non-invasive way. Further, by taking a translational approach, these findings can be related to animal and genetic studies, increasing the understanding of the complexity of a developing brain.

2.2.2 Neural origins of EEG.

Electroencephalography (EEG) is a non-invasive method of recording electrical activity of the brain, which is picked up via electrodes placed on the scalp (Pizzagalli, 2007). The signal is thought to be generated by cortical pyramidal neurons in the cerebral cortex, which are perpendicularly oriented relative to the brain surface. The activity that is detected at the scalp is a summation of excitatory and inhibitory postsynaptic potentials of large populations of neurons. Post synaptic potentials are the by-product of neurotransmitter binding to post-synaptic cells. As the charge travels from dendrite to the cell body, a dipole is generated (a difference in electrical charge separated by a small distance, (Luck, 2014)). This potential is large and long-lasting, with the summed voltage being large enough to be picked up at the scalp surface. Action potentials, or electrical charges that travel from the axon to the terminal buttons, are also involved in generating neural activity, although they are too short to be recorded (Louis et al., 2016a). Further action potentials in axons have opposing charges and cancel each other out. Therefore, EEG activity is generated by post-synaptic activity.

It should further be noted that voltage recorded from the scalp is a relative value (typically microvolts, μV), such that it actually represents the difference between the measured

electrode and a reference electrode which is placed somewhere else on the head. This is often hard to interpret directly as the microvolt value will change depending on the type of analysis conducted, including filtering, baseline correction and choice of reference (time frequency analyses also transform the original data scale). These values can also differ based on individual cases (i.e. skull thickness or hair structure), although this is of less concern when interpreting data from very young participants with relatively thin skulls and minimal hair. Nonetheless, these changes affect all trials and all participants in the same way, meaning that the results can still be interpreted in a meaningful way (Cohen, 2014).

EEG signal contains task relevant and task irrelevant neural activity. Based on the assumption that task-irrelevant noise occurs randomly throughout the whole trial, task relevant activity is time-locked to presentation of the stimulus. This has formed the general principle behind the ERP technique and, more recently, evoked oscillations, that averaged activity over many trials contains the response to the stimulus only (David et al., 2006; Luck, 2014). Brain oscillations reflect more of the stimulus-driven dynamics of the EEG signal and will be heavily featured in the chapters to follow.

Due to issues of background noise in EEG data, the paradigms described in both parts of this thesis only consider brain activity which is time and/or phase locked to presentation of auditory stimuli. The combination of signal processing techniques of within both time and frequency domains is used to achieve a comprehensive understanding of brain specialization mechanisms, which is limited when only a traditional ERP technique/resting state power are used.

2.2.3 Exploring the dynamic nature of the EEG signal.

While the origins of the signal may be traced back to a single source, there are conceptual distinctions to be made in the analysis and interpretation of the different analysis methods. Several aspects of the neural signal are examined in this thesis, which captures early

individual variation within typical development, age-dependent change and group differences based on elevated likelihood of neurodevelopmental disorders.

When data from multiple participants and/or conditions is averaged together to produce a grand average event-related potential (ERP) waveform, the result is represented as a voltage value at each time point (Luck, 2014). The waveform is described according to latency and amplitude, with the resulting peaks and troughs in the waveform defined as separate components (Hoehl & Wahl, 2012; Sur & Sinha, 2009; Woodman, 2010). These are associated with certain aspects of perceptual processing, attention, and cognition based on changes in electrical activity during performance of the respective tasks (Hillyard & Picton, 2011; Walter, 1938). Due to the high temporal resolution of the ERP technique highlighted in the above sections, this method remains one of the most widespread tools used by psychologists and cognitive scientists. Irrespective of its advantages, visualizing the waveform in time only fails to reflect the dynamic nature of the signal and is not able to reveal information about the underlying neuropsychological mechanisms which may be involved the generation of that signal (Cohen, 2014).

On the other hand, EEG spectral power is a frequency-dependent measure of the voltage from the scalp, which records rhythmic activity from populations of neurons. It reflects increases or decreases in the probability of an individual neuron to fire during a specific time during an oscillation, and contributing in many ways to the morphology of the ERP waveform (Makeig et al., 2002; Makeig, Debener, Onton, & Delorme, 2004). Oscillations have been identified as an essential neural mechanism which underlies synaptic, cellular and higher-order brain functions, which is particularly important when investigating neural processes across developmental time.

Different frequency bands have been associated with different functional processes i.e. alpha (7-12Hz) and attentional processes and inhibition (Klimesch et al., 1998; Klimesch,

Sauseng, & Hanslmayr, 2007; Orekhova, Stroganova, & Posikera, 2001); beta (12-30Hz) and attentional activation and preparation and execution of voluntary movement (Gola et al., 2013; Hanslmayr et al., 2007; Nam et al., 2011); theta (4-7Hz) and memory function, emotional regulation and salience detection (Aftanas et al., 2004; Bosseler et al., 2013; Knyazev, 2007); delta (<4Hz) and motivation and reward seeking (Knyazev, 2007); and gamma (30-50Hz+), which has been associated with perceptual binding and higher-order information processing (Bartos et al., 2007; Buzsáki & Wang, 2012; Tallon-Baudry & Bertrand, 1999) as well as atypical processing in individuals with developmental or neurological disorders (Hall et al., 2011; Orekhova et al., 2008; Roach & Mathalon, 2008; Wang et al., 2013). It should be noted that the exact frequency bands are attenuated in younger infants, and become adult like by mid-childhood (Marshall, Bar-Haim, & Fox, 2002). Using time-frequency analyses further allows to tap into task-relevant dynamics of the EEG signal, which are occluded by the gross averaging method of ERPs.

Of note, there are two main limitations of the time-frequency method (Cohen, 2014). Due to the general properties of rhythmic signals, there is a loss of temporal precision during time-frequency decomposition, with lower frequency bands suffering from higher loss of temporal accuracy. However, this does not decrease the overall utility of the analysis as (a) although some precision is lost, time-frequency analyses will still maintain higher resolution than that of fMRI, and (b) the temporal precision of ERPs is often not utilized as common components such as P1 and P3 are defined broadly over a 50-150ms period. Additionally, due to an increase in the number of variables considered for analysis, the time-frequency approach comes with added complexity, which can often reduce power to detect specific effects. In order to reduce this possibility, an *a priori* approach was taken for both the design and analytic strategies of the tasks described in this thesis. Specifically, this involves outlining the exact variables of

interests and statistical tests by pre-registering the analysis pipeline before data processing commences (see Chapter 2.6 for description of this process).

2.2.4 Challenges for developmental research.

Infant research has its unique challenges. During EEG application, the child sits on the parent's lap, while the researchers attempt to distract their attention with toys and bubbles. This is more easily achieved in younger infants who are not yet crawling or walking, and becomes increasingly difficult with age. If the infant becomes bored, snacking on soft crackers is permitted, although this may introduce artefact into the data. Due to these challenges, attrition rate of the infant population ranges between 35 and 75% (de Haan, 2013). It is therefore essential that the experimental procedures are consistent and that care is taken during net application to insure high quality of EEG signal.

After data collection is complete, a significant amount of time is required to process EEG data. This includes removing portions of the signal contaminated by gross motor artefacts and eye blinks, which is significantly higher in infant populations to that of children and adults (Georgieva et al., 2017). Although it is common to use algorithms to manipulate the data, this may interfere fundamentally with the activity that is being measured. For example, eye-blink correction algorithms may filter out maturational change in frontal EEG power (Somsen & van Beek, 1998). Independent Component Analysis (ICA), which has been shown to be a powerful tool in artefact removal from biosignal in adults, may add noise and correction errors to data with fewer trials (and thus lower signal-to-noise ratio; (Haumann et al. 2016; Kampis et al., 2016)). Therefore, data discussed in this thesis is selected from artefact-free signal only.

More generally, this thesis features data from special populations, i.e. infants with a genetic disorder and those with elevated familial likelihood of ASD and/or ADHD. Ethical considerations of working with these populations must include additional safeguards (Modi et al., 2014; Webb et al., 2013). Specifically, adequate provisions have to be made for parents or

guardians, especially as they may also be affected by a genetic or neurodevelopmental condition themselves, and ensuring that any possible risk is outweighed by the benefit of their participation. Researchers have to be sensitive to potential delays in physical or cognitive development of infant populations, and ensure that the testing protocols are appropriate for individual levels of ability. Further, there may be differences in head shape/size associated with genetic and developmental disorders such as Downs Syndrome, Williams Syndrome and Neurofibromatosis Type 1 (Tonsgard, 2006; Trauner et al., 1989), which should be taken into account when selecting equipment and conducing the experiments.

2.3 EEG Data Acquisition

2.3.1 Hydrocel Geodesic Sensor Net.

EEG activity from the scalp surface is typically recorded simultaneously through a number of electrodes placed on the scalp. For the tasks featuring EEG technique (i.e. EEG Task 1 Chapter 4 , EEG Task 2 in Chapter 5 and EEG Task 3 in Chapter 6), a Hydrocel Geodesic Sensor Net (Electrical Geodesics Inc., Oregon, US) was used, with an array of 128 silver-silver chloride electrodes plus a reference electrode. Within this array, each electrode is encased in a sponge that is wetted with liquid electrolyte solution (water, shampoo, and potassium chloride) during operation, with a soft plastic pedestal, mounted onto an elasticated webbing. The sensors are held in a tension structure which stretches over the head, ensuring correct spatial distribution over the scalp. This type of technique allows large numbers of electrodes to be applied quickly to the scalp surface (Tucker, 1993), without any abrasion or need for gel application, making it especially useful in the study of infants (Figure 2.1). This is accompanied by short preparation (10 minutes) and application (less than 1 minute) times.

Figure 2.1 Infant wearing Hydrocel Geodesic Sensor Net, taken after EEG recording session.

2.3.2 EGI amplifier.

Data for all the tasks reported using the EEG method was acquired using the EGI NetAmps 300 EEG Amplifier. This is a differential amplifier, which means that it measures and amplifies the difference between voltage at each individual sensor site and the reference (in this array is the vertex electrode Cz). Therefore, the voltages measured are relative rather than absolute values, which are then amplified. The signal is then digitized to an analogue/digital (A/D) converter, which allows the data to be stored and processed offline. A 0.1-100Hz band bass filter was used, with a sampling rate of 500Hz for EEG Tasks 1 and 2 (Chapter 4,5) and 1000Hz for Task 3 (Chapter 6). Sampling rate is the rate of conversion of signal from analogue to digital, and must be higher than the Nyquist frequency (at least twice the speed of acquisition relative to the highest frequency of the signal of interest). The sampling rate was higher for the 14-month-old infants featured in Chapter 6 due to the update of amp.

The reference sensor in the chosen array is located in a central location on the scalp, which means that it is not affected by hemispheric asymmetry, or bias between right and left hemisphere or frontal and posterior sites. During recording, the signal was re-referenced to the

average reference, which is the average of neural activity in all 129 sensors. This introduced a constrains that the sum of activity across all electrodes should equal to zero, following the principles of Ohm's Law (all electrical potentials are dipoles with positive and negative potentials). This is an accepted technique when using high density channel arrays (Tucker, 1993).

2.3.3 Electrode impedance.

As an additional consideration of using this technique, the signal needs to be free from environmental noise. This is typically achieved by obtaining good electrical contact with the scalp, and can be done by passing low currents through the electrodes and measuring the resistance to the flow of the current, also known as impedance. The higher the impedance of the electrode, the smaller is the amplitude of the EEG signal due to contamination from environmental noise. It is therefore a practical decision taken by some researchers to detect electrodes with high impedances prior to the start of the EEG protocol, which can then be adjusted for improved contact with the scalp and improved quality of signal (Louis et al., 2016b; Picton et al., 2000).

However, the process of checking electrode impedance requires additional time at the beginning of the recording session, which is not easy to achieve with the more demanding infant populations. An important benefit of the EGI system used for the experiments described below is that it allows for high-input impedances (typically in the 50–100 kΩ range), with no special preparation or electrolyte gel required for administration. Further, majority of infants have very little/no hair and do not have hair treatments beyond basic shampoo, which allows the electrodes to have close contact with the scalp and impendences are kept sufficiently low for recording. As such, impedance checks were skipped prior to recording, and this has been adopted in the field to maximise participant compliance (Johnson et al., 2001). It should be noted that the overall quality of the signal (i.e. excessive noise due to electrical/magnetic

sources, signal drift, excessive number of channels which are flat or stuck at maximum amplitude) was inspected prior to the commencement of each recording session, and measures were taken to improve, permitting these measures would not distress the participant or parent.

2.4 EEG Pre-processing

Data was analysed offline using Netstation 4.5.7 analysis software (Electrical Geodesic Inc.), using the steps described below.

2.4.1 Filtering.

As stated previously, EEG net not only records brain activity, but can also detect skin and movement potentials as well as line noise from the surrounding electrical equipment (i.e. slow waves below 0.1 Hz are associated with skin and movement potentials, and line noise is 50Hz in the UK). For the studies reported in this thesis, a bandpass of 0.1-100Hz was used during online recording. The data was then filtered offline with a 0.1Hz high pass and a 100Hz low pass filter. A fairly liberal range is to be retained at this stage, where additional filters can be applied later if necessary. Any activity which falls either above or below this set criteria is not considered to be brain activity.

Additionally, a 50Hz notch filter was applied to the data off-line. This is an aggressive filter which removes power at a specified narrow region of the spectrum, which is done with minimal disruption to the rest of the signal. Although applying a notch filter is debated in the literature (Luck, 2014), it allows higher retention of the data and is therefore highly useful in populations where data quality is an issue or those with moderate to low sample sizes.

2.4.2 Segmentation.

After the data has been filtered, it was segmented into short epochs that are time-locked to the onset of the presented stimuli. This is done to isolate neural activity (i.e. auditory evoked potentials), which immediately follow presentation of the sound stimulus. The segment lengths

chosen for Task 4, 5 and 6 were dependent on the components of interest and inter-stimulus intervals and are defined further in the respective chapters. It should be noted that at least 200 milliseconds had to precede the onset of the stimulus in order to form an appropriate baseline for wavelet analysis and 100 milliseconds for analysis of ERPs.

2.4.3 Artefact detection.

Following offline filtering and segmentation, the resultant epochs were subjected to automatic and manual detection and removal of visible artefact. This process is essential in analysis of EEG data, as the net records electrical activity from the skin and muscles. Presence of artefacts is more likely in the data due to the increased movement of the infant participants. There are four main artefacts of concern to EEG signal, including eye blinks and eye movements (saccades), larger movement potentials and alpha activity. The first analysis step included an automatic artefact detection tool which carried out preliminary identification of bad channels, eye blinks and movements (for Threshold Artefact Detection settings used see Appendix A). Following this, visual inspection of the signal at each electrode (trial-by-trial) was carried out, where any potential errors made by the automatic artefact detection tool were corrected.

2.4.3.1 Eye blinks.

Eye blinks can significantly contaminate the EEG signal, particularly in the frontal electrodes. This contamination can have a profound effect on interpretation of the results from those electrodes, specifically if it coincides with presentation of the stimulus. The eyeball itself acts as a dipole, with a positive pole at the front and a negative one at the back of the eye. During an eye blink, the eyelid passes over the eyeball and generates a sharp negative deflection in voltage, which is picked up by the frontal electrodes. The infant version of the Hydrocel Geodesic Net only has electrodes at the top half of the eye region (rather than above and below the eye, as featured in the adult setup). However, it is still possible to identify eye-

blink contamination in the data and discard the trials and/or channels affected. There is an important trade-off in infant research in that infants blink much less than adults, but also their evoked potentials tend to be much greater in voltage amplitude (this further increases the signal-to-noise ratio in this population). It has also been reported that greater amount of eye activity is necessary to contaminate infant EEG (Nelson, 1994).

Findings from the present study are less likely to be affected by eye blinks, as activity in electrodes closest to the eyes and forehead is not examined. Additionally, the stimuli presented were auditory in nature and would only coincide with eye-blinks if the infant was particularly sensitive to auditory stimulation.

2.4.3.2 Eye movements.

One of the biggest challenges of infant EEG recording is that participants cannot be told to stay still or fixate on a certain object on the screen. This means that eye movement artefacts are prevalent in the data, which is further enhanced by their increased motivation to visually explore the new surroundings of the recording room or seeking out the mother or the researcher. Eye movements in infants are also not fully understood, with microsaccadic movements potentially contaminating the recordings (Köster, 2016). Although microsaccades are not the prominent cause of concern in auditory paradigms, this issue will be addressed with statistical comparisons within the relevant chapters (Kampis et al., 2016). For the auditory paradigms described later in this thesis, eye movements are a cause of concern as they are frequently accompanied by gross movement of head and arms, and attracting the infant's attention to a certain object/experimenter allowed to reduce both eye and head movements. As mentioned previously, a lot more saccadic movement is required to contaminate infant rather than adult EEG signal (due to thinner skulls in infants, with reduced cell packing in the brain), giving rise to higher signal-to-noise ratio (Nelson, 1994).

Several measures were taken in order to maintain attention in infants throughout the EEG recording. The room was dimly lit and all furniture and equipment, apart from the screen, were covered with black or grey material to reduce the novelty and interest of the room's features to the infant. Further, an experimenter was always present in the testing room and engaged the infant in silent play during presentation of the auditory stimuli. Based on the 'free play' setting of the experiments described here, it was highly difficult to eliminate all eye movements. This was addressed in offline processing of the data, whereby if saccadic activity was present in a given epoch, it was marked as 'bad' and not included in the final average.

2.4.3.3 Movement potentials.

As described above, increased muscle activity creates issues when dealing with infant EEG data. In order to reduce movement during the 'free play', parents were instructed to hold her infants at the waist, keeping them upright and not bouncing their legs. However, this was not fully achievable, as infants were allowed to reach for and handle objects. Movement artefacts were addressed in visual inspection of the data, where trials were marked as 'bad' if activity was of a disproportionally large amplitude (below -100 and above 100 microvolts), usually associated with postural shifts and not neural activity. With some small types of movements, only a few electrodes were contaminated, and this case is discussed in more detail below.

Dealing with movement potentials is particularly important when looking at higher frequency oscillations. Intracranial EEG recordings have suggested that oscillations associated with the gamma band are closely linked with ocular and large muscle activity when recorded above the scalp surface (Jerbi et al., 2009; Pope et al., 2009; Schwartzman & Kranczioch, 2011). Special considerations have to be taken here (i.e. excluding trials where there is obvious movement of the head and or trunk), in order to minimize EMG signal contamination. Further, isolating activity which is time and phase-locked to stimulus presentation allowed more

accurate conclusions to be made about higher frequency oscillatory activity in the brain (David et al., 2006; Longo, 2000).

2.4.3.4 Alpha waves.

Alpha activity in the brain occurs around 10Hz in the brain and is characterized by its sine morphology, and most commonly recorded when the participants are tired. Up to 12 months of age, alpha band activity is visible at around 7Hz (Smith, 1941). This can be problematic when investigating time-locked activity such as ERPs or evoked brain potentials, as it can become entrained to the presentation of the stimulus and survive the averaging process.

The most efficient way of reducing alpha contamination in EEG recordings is ensuring that the participant is well rested. This is particularly challenging with infants, as tiredness can occur very quickly, especially in the context of a long testing protocol. For the experiments described below, the EEG sessions were scheduled around the infants' regular sleeping schedule (either after the morning or afternoon nap).

Substantial alpha contamination can occur in the absence of participant tiredness. Specifically, the alpha rhythm can become entrained to stimulus onset if it presented at a constant rate (as it is in EEG Task 3, Chapter 6). In order to reduce this, a jitter (inter-trial stimulus interval) was introduced between the trials, which to some degree randomized stimulus onset (Luck, 2014).

2.4.4 Bad channel replacement.

During visual inspection of the data, neural activity at the individual channels which appeared to be extremely noisy and not comparable to the surrounding electrodes in its morphology was marked as 'bad'. Subsequently, values for these channels were replaced with an average voltage of the surrounding nearby electrodes. This is done based on the assumption that in high-density acquisition nets surrounding electrodes carry similar data.

2.4.5 Baseline correction.

All the cleaned epochs were then baseline corrected. This is an essential step to ensure that the activity reflects a response to a stimulus versus general activity going on in the brain. This step does not alter the signal, but simply shifts the waveform up or down to bring the pre-stimulus activity close to zero voltage.

For the tasks described below, baseline correction was performed by taking an average voltage of pre-stimulus activity, and subtracting it from the entire length of the post-stimulus epoch. Typically, the baseline period of 100 milliseconds pre-stimulus is considered sufficient in ERPs, however, this is extended to 200 or 500 milliseconds for time-frequency representations, depending on stimulus type (Luck, 2014; T. W. Picton et al., 2000).

2.4.6 Re-referencing.

The clean epochs were then re-referenced to the average reference through the Montage Operations tool in Netstation. Note that the number of channels is not downsampled here, as the average was specified between all channels in the array.

Re-referencing is an important concept in EEG signal processing, as the reference point chosen during online recording is usually arbitrary and no single site can be assumed to carry a constant value throughout the course of the recording. The data described below is re-referenced to the average as the high number of channels allows us to sample the scalp surface evenly, resulting in an average value that is close to zero (based on the assumption that the signal is dipolar and the surface integral should be equal to zero).

2.4.7 Averaging procedures.

The first step of obtaining an average of all neural responses involved individual averaging of all good trials for each condition in the task (i.e. those not excluded artefact detection). These trials were pooled together to produce a composite of the neural response

time-locked to presentation of each stimulus. The averaging process means that background EEG is reduced, while neural activity related to the stimulus is isolated.

Next, a grand average waveform (ERP) was computed by collapsing the individual data in each condition. This allowed the data to be visualized and compared between groups. Then the data was exported into Matlab® (2017a) for spectral decomposition, which is described in the next section.

2.4.8. Time-frequency analysis.

The purpose of time frequency analysis is to understand the dynamic nature of EEG signal and how it changes with time. This work features different variations of wavelet decomposition (time-frequency analysis) in Chapters 5 and 6. In this section, I discuss time-frequency analysis as it is relatively novel in infant literature and can provide important additional information beyond what is permitted by traditional ERPs (Isler et al., 2012; Makeig, 1993).

The wavelet approach was originally developed by Jeong and Williams (1990) and demonstrated that using variable window spectrograms reveals unique mathematical and physical aspects of any signal. As with other methods of spectral decomposition (Fast Fourier Transform (FFT), Short-FFT), wavelet methodology allows to separately quantify magnitude and phase information from the EEG. The general advantages of the time-frequency approach over ERPs are discussed in Chapter 2.2.3, while this section will describe and evaluate the more practical concerns of using wavelets. This is a particularly fitting approach to the investigation of neural specialisation in infants, as previous investigations report that pre-verbal responses to simple tones and linguistic stimuli can predict later language and developmental outcomes (Cantiani et al., 2016; Choudhury & Benasich, 2011).

Essentially, wavelets are sine waves which are windowed with Gaussian tapers to create smooth edges (see Figure 2.2). This means that wavelet convolution can be visualised as a vector between the original wavelet and the EEG data (i.e. a point within the spectra-temporal space). For the purposes of analysis featured in Chapter 5, Morlet wavelets are used as they are most common in time-frequency analyses (Cohen, 2014; Isler et al., 2012; Roach & Mathalon, 2008). Within the generated vectors, higher values suggest increased power at a given frequency and lower values reduced power at a given frequency. Note that the signal in Figure 2.2 has been artificially generated and that the response of 'true' EEG signal is much more dynamic.

There are important distinctions which have to be highlighted in the analysis of spectral activity, namely the conception of evoked, induced and ongoing oscillations. The three different types of activity are assumed to reflect different neural mechanisms and differ based on the degree of phase-locking to the onset of the stimulus (Galambos, 1992). *Total power* is calculated by taking an average of the power values from time-frequency decomposition, and while it is commonly used in the field of cognitive electrophysiology, it comprises both task relevant and irrelevant information. *Evoked power* is defined as activity which occurs at the same latency and in the same phase relative to stimulus onset, and more commonly believed to underlie early evoked ERP responses (calculated though subtraction of non-phase-locked power from total power). On the other hand, *induced power* is thought to be correlated with the stimulus, it is independent of the latency and phase (revealed when phase-locked components are subtracted from the EEG signal in single trials). Nonetheless, these distinctions are unlikely to be absolute, with common structural mechanisms affecting evoked and induced oscillations (David et al., 2006).

Lastly, time-frequency analyses also allow the separation of power and phase information. This is derived from computing the consistency in phase-locking of oscillatory

signals across trials, and reflects temporal and spectral synchronisation of the signal. Activity that is phase-locked to presentation of the stimulus and also represents the inter-trial variability in neuronal activity, which is averaged out in traditional ERP technique. The inter-trial coherence or ITC value summarises the extent to which phase values are clustered over trials. These values cannot be averaged together (Cohen, 2014; Herrmann, Grigutsch, & Busch, 2005), but instead are represented as the average vector and taking the length of the vector, which has a unit length between 0 (no phase clustering) and 1 (all trials are clustered around one phase angle).

Comparing phase coherence values have been used to provide more information about evoked activity and associating differences in ITC with atypical neural synchrony in cases of atypical auditory processing (Nash-Kille & Sharma, 2014; Thatcher et al., 2009). Analysis of power and phase information has been prevalent in inter-cranial recordings of animal brains, and more recently adapted within the EEG setup within the human population.

It has been shown that oscillations and ITC correlate within several frequency bands (i.e. gamma and theta) are associated with specialisation towards the native language as early as 6 months (Ortiz-Mantilla et al., 2013) and may be used as putative marker of atypical cortical function in infants with elevated likelihood of developmental disorders (Kolesnik et al., 2019). It should be noted that ITC values are distinctly smaller in young infants (i.e. between 0.005 and 0.3; Bishop, Anderson, Reid, & Fox, 2011; Edgar et al., 2016; Nash-Kille & Sharma, 2014; Ortiz-Mantilla et al., 2013) and increase steadily with age to reach adult levels (Bishop, Anderson, et al., 2011; Muller, Gruber, Klimesch, & Lindenberg, 2009). It has been used increasingly in studies of auditory processing to supplement frequency transformations (Ortiz-Mantilla et al., 2013, 2016), although the strongest responses appear to be in the lower

frequency bands (Musacchia et al., 2017). There is still limited understanding of infant ITC responses, this will be treated as an exploratory analysis in Chapters 5.

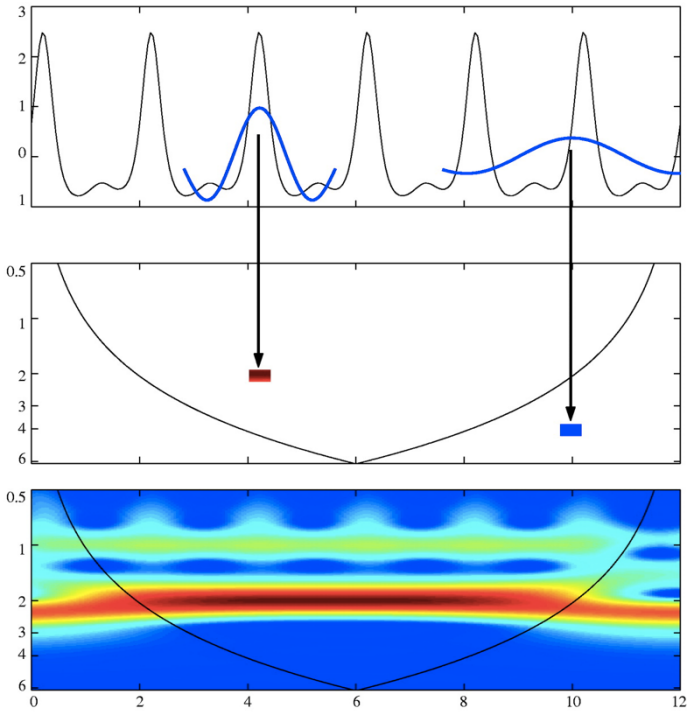

Figure 2.2 Example of wavelet convolution method based on very regular signal superimposed with scaled versions of the Morlet wavelet. The curved line shows temporal distortion created at lower frequencies when a higher cycle is specified. Adapted from Cazellez et al. (2007).

2.5 EEG Data Analysis

Prior to statistical analyses of the processed data, the temporal and spatial regions of interest (ROIs) were identified. Note that the time-frequency approach will require different time regions of interest and also the pre-specification of the frequency bands of interest.

2.5.1 Identifying spatial regions of interest.

For all EEG tasks described in this thesis, different spatial regions are selected based on existent literature. Auditory responses are commonly characterised by strong responses in the frontal and central regions (Kushnerenko et al., 2002; Stefanics et al., 2007), although tasks which employ time-frequency analysis will also discuss responses in the tempo-parietal regions, where they have been identified in recently emerging studies (Musacchia et al., 2015; Roach & Mathalon, 2008; Rojas et al., 2008). In the tasks described in this chapter, the spatial ROIs were defined based on existent literature in both adult and infant studies (Guiraud et al., 2011; Musacchia et al., 2017; Risto Näätänen et al., 2011; Orekhova et al., 2008) and later confirmed though visual inspection of the grand averages of ERP and spectral responses across the whole scalp. Existent literature was an important guide as to where responses are expected in a particular age group/towards a particular stimulus, as averages of data from populations with neurodevelopmental disorders may reduce the strength/show different topology to that of the expected effect (see Figures 2.3-2.5).

Due to the high density of electrodes in the EGI system used, it is advised that a cluster of electrodes is chosen per area of interest rather than a single electrode (de Haan, 2013; Luck, 2014). Therefore, between 4 and 6 neighbouring electrodes were chosen per cluster to generate an average waveform/spectral plot in each of the experimental conditions. During visual inspection of the responses in each of these clusters, a positive-going potential was expected in the 100-150ms range resembling the P150 response with a negative-going potential 100-250ms resembling the mismatch-negativity response in the grand average waveform, however these time regions are largely driven by the type of stimulus and age of participants (Marshall et al., 2002; Näätänen, Pakarinen, Rinne, & Takegata, 2004). Additionally, a clear increase in spectral power in the higher frequency band (20Hz+), corresponding to an increase in gamma oscillatory activity, was expected within the chosen electrode clusters for both tasks. It was

further expected that the nature of the response will be different in each cluster based on the type of analysis, i.e. stronger ERP responses in the frontal areas vs. higher oscillatory activity/power in the tempo-parietal areas. The electrodes chosen fulfilled these criteria.

2.5.2 Identifying temporal regions of interest.

Identification of the temporal windows of interest for the tasks discussed in this thesis was complicated by the large variability presented in existing literature. This is due to the effects of developmental changes which occur within the morphology of the infant EEG responses within the first years of life (Kushnerenko et al., 2002; Tierney et al., 2012). Therefore, the time-windows selected for analysis were based on (1) current infant literature and (2) group grand average waveforms in order to capture variation in waveform peaks and 'bursts' prevalent to oscillations in the higher frequency bands. It should be noted that these regions varied slightly between the different types of EEG signal processing (i.e. within the auditory domain, ERP responses tend to be stronger in the fronto-central regions while time-frequency responses have been recorded in fronto-central and temporal regions).

2.5.2.1 Timing correction.

One issue prevalent to auditory EEG experiments is sound latency, which must be verified. There is a delay of EEG signal acquisition inherent to the EGI GES 400 series amplifier used in data collection. The stimulus offset was set to 66s during the segmentation stage, based on Electrical Geodesics Inc. Advisory Notice on EEG timing (23/03/2016). Therefore, any further atypicalities in the grand average were likely to indicate issues between the auditory digital input marker (DIN; sent to online EEG recording relative to the onset of the stimulus itself). In order to address this, the precision of auditory-stimulus presentation was tested using an AV Device following the technical manual (Electrical Geodesics, Inc., 2007), and results were visualised using the Event Timing Tester program, which provided the relative time between the DIN marker and condition marker (i.e. Standard 1) as well as elapsed time of

the task. Timing tests were run on eight test files that revealed progressive changes in the delay with which markers were sent to the raw EEG recording. A regression equation was created based on this test that allowed condition markers to be corrected to the DIN marker, which was then applied to all the data files in MatLab® (in-house scripts by E. Jones). Following this, the data was averaged and exported for further analysis.

2.5.2.2 ERP.

In order to select an appropriate temporal window, several previous publications which looked at auditory processing and change detection were considered. In a comparison of child and adult habituation responses, habituation effect (i.e. reduction in amplitude of response with repetition) was identified between 100 and 200ms with higher amplitude and faster reductions in adult participants (Muenssinger, Stingl, et al., 2013). Guiraud and colleagues (2005) found that neural habituation to auditory stimuli in infants elicited a change in a key component P150 from 110-250ms post stimulus presentation, versus auditory change responses were characterised through a P150 (90-170ms) and MMN (120-320ms) responses in the frontal and central areas. The finding was also replicated with repeated language stimuli between 100-250ms (Ortiz-Mantilla, Hämäläinen, & Benasich, 2012; Seery, Vogel-Farley, Tager-Flusberg, & Nelson, 2013; Seery, Tager-Flusberg, & Nelson, 2014). Note that Ortiz-Mantilla and colleagues used source localisation to identify the P150 and a later negative component (around 400ms post stimulus) in both the frontal and temporal scalp regions, with frontal activation preceding temporal cortex responses. Source localisation is more robust to noise by mapping out the origin of the signal on the scalp surface, which solves the inverse problem (Luck, 2014) prevalent in analysis of EEG signal.

On the other hand, change detection was initially characterised in adults through a mismatch negativity response (i.e. MMN, a negative going component peaking 150-250ms post stimulus) between the common standard and an auditory oddball (Näätänen et al. 2004).

In younger infants, auditory processing to spectrally rich, non-speech sounds is characterised by an early negativity (EN: 150-220ms) a large positive component (PC: 250-300ms) and a later negativity (400ms+) (Kushnerenko et al., 2007). These responses decrease in amplitude in the first months of life. It is suggested that this decrease reflects inhibition of processing of uninformative information from the environment. Infant studies revealed that the P3 may be an index of auditory attentional engagement, which a pre-requisite of later learning and language acquisition (Kushnerenko et al., 2002; Kushnerenko, Bergh & Winkler, 2013). In adults (Polich, 2007) and children (Čeponienė et al., 2004; Gumenyuk, et al., 2003) a distinct positive component is recorded fronto-centrally around 300ms from stimulus onset, which is associated with the infant P3. It was suggested that this response reflects evaluation of contextual relevance of the rare/complex auditory stimulus.

2.5.2.3 Time-frequency analysis.

The choice of the temporal window to be used in time-frequency analyses was largely based on the length of the oscillation within a pre-specified frequency band as well as the type of response used (i.e. oscillation in the gamma band is fast and therefore will appear in a shorter time window than alpha/theta, which are slow waves and responses are visible over 1.5-3 seconds). There are several approaches that have been used in research with time-frequency and frequency analyses, including visual inspection, hypothesis-driven statistical comparisons across conditions, or subject-specific time-frequency windows (Cohen, 2014). For the purpose of tasks described in this thesis, temporal regions of interest were selected based on previous literature and a grand average plot of the signal (averaged over group and condition), in order to avoid over-manipulation of the data.

For analysis of evoked responses in the gamma range (Chapter 5), which is the primary frequency of interest, temporal region of interest was defined as 50-150ms for early evoked responses (Rojas et al., 2008). Analyses were also carried out in the later time window that is

thought to capture induced gamma power (200-400ms); which is important to study due to previous reports of associations between individual variability in frequency peaks, genetic growth factors (Smit et al., 2012) and GABA concentration (Muthukumaraswamy et al., 2012).

The wavelet analysis in EEG Task 2 (Chapter 5) was performed using WTools (developed by Parise, Filippin, & Csibra, available upon request), which extracts amplitude (square root of power) as it was part of a previously published investigation. On the other hand, wavelet analysis for EEG Task 3 (Chapter 6), via a wavelet decomposition in Fieldtrip (Oostenveld et al., 2010) following custom built scripts (by E. Jones). This technique is used to detect event-related spectral perturbations (ERSPs; Makeig, 1993) in epoched datasets (see Chapter 6.2 for details of the procedure). The frequency bands of interest in this task was selected based on previous literature as well as visual inspection of the grand average of all participants and conditions to account for 'spectral leakage' or smearing following convolution with the wavelet (Kay, 2013).

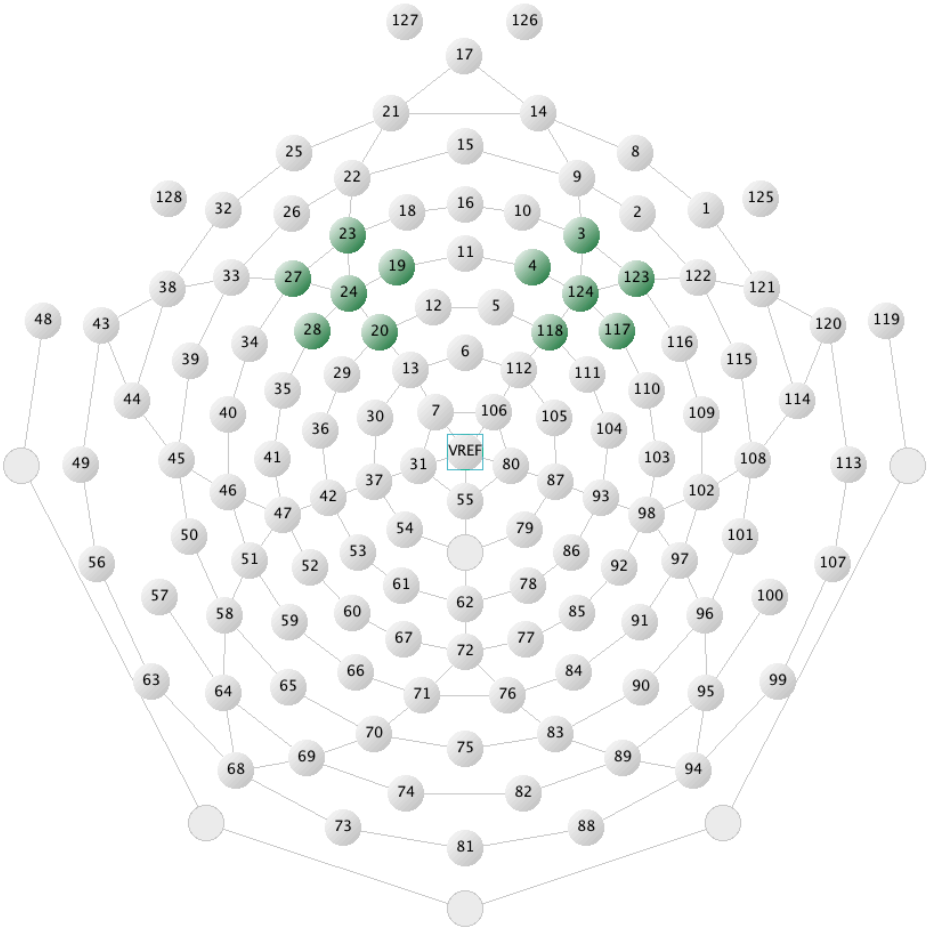

Figure 2.3 Location of electrodes used for analysis in EEG Task 1 Chapter 4.

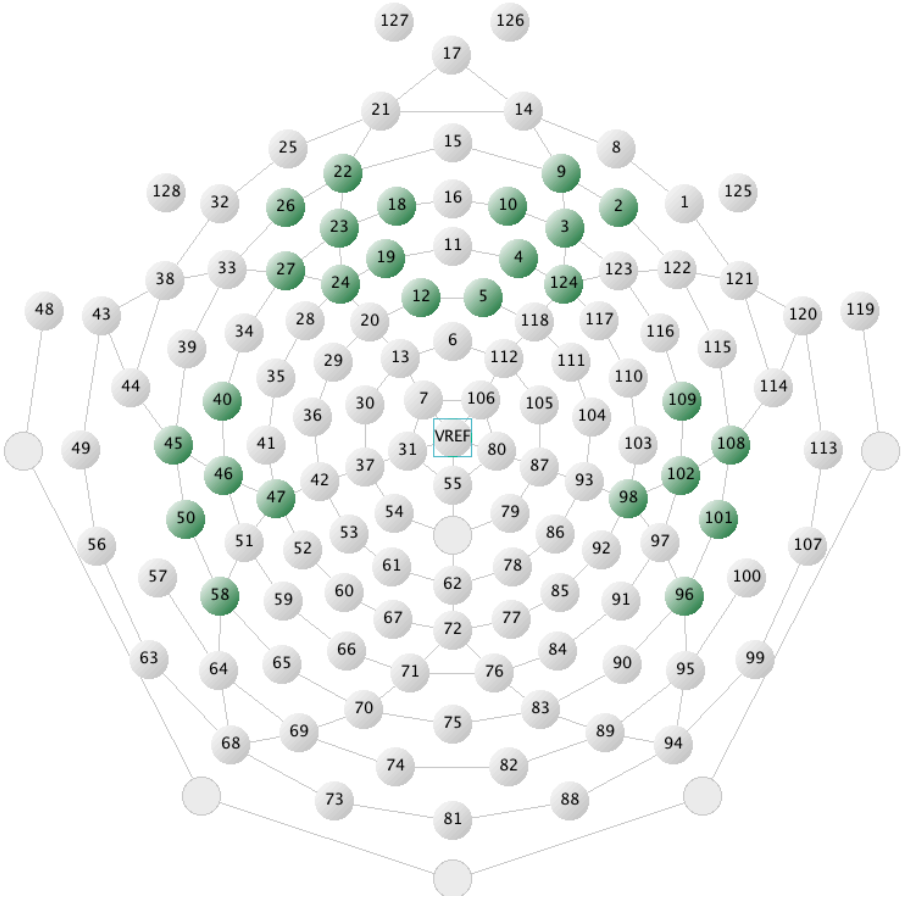

Figure 2.4 Location of electrodes used for analysis in EEG Task 2 Chapter 5.

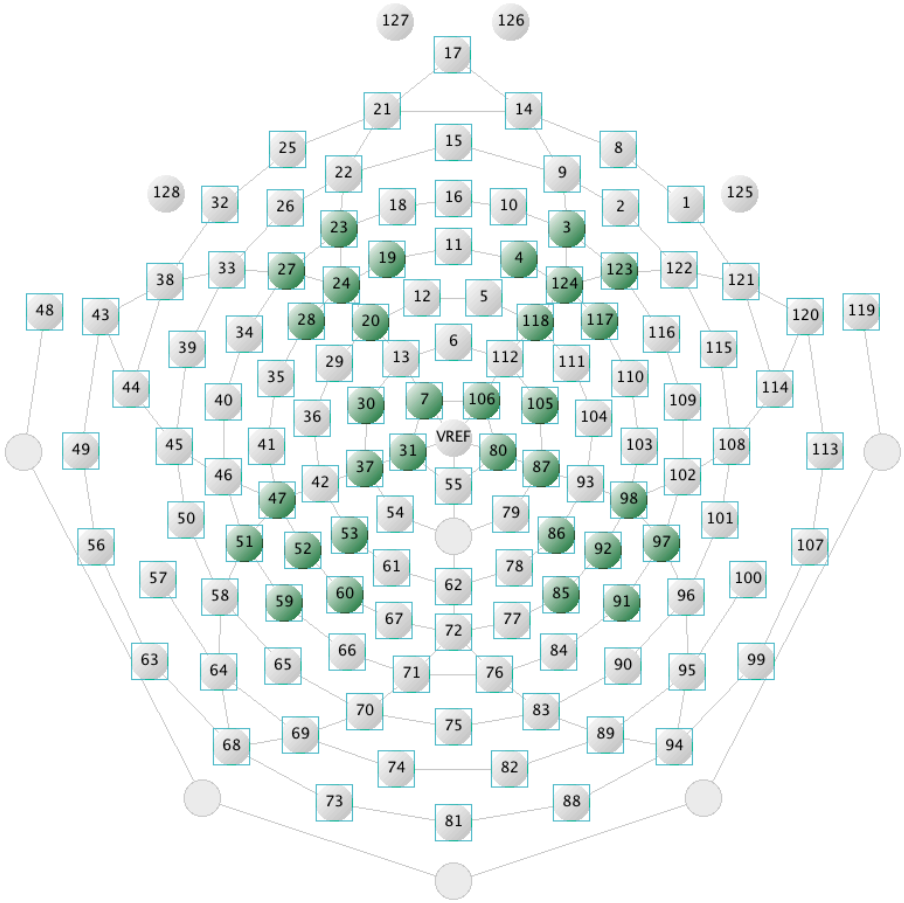

Figure 2.5 Location of electrodes used for analysis in EEG Task 3 Chapter 6.

2.5.3 Statistical analyses.

As previously stated, grand average ERP waveforms are generated from a grand average of the individual averages per condition. Statistical analyses that are most common for ERP analysis are peak amplitude and mean amplitude analyses. Peak amplitude measures the voltage of highest peaks (both negative and positive) in the EEG signal and are mainly used in the analysis of adult data. This is because the peaks are more well defined and represented in literature. A more suitable approach for the analysis of infant ERPs is mean amplitude analysis, which involves taking the average voltage of a waveform within a specified time window. This is particularly useful when peaks are less defined and/or when there is individual variability in presentation of the peaks.

The main disadvantage associated with using mean amplitude analysis is that there is reduced certainty as to the timing of the neural activity within the chosen time band. This means that the number of statistical tests would need to increase to isolate the effect, thereby increasing the likelihood of a type I error. As ERP analysis are not the main or only focus of the present thesis, there was minimal statistical manipulation of the data.

For wavelet analysis, average of power values per individual per condition were included in statistical comparisons. The number of statistical comparisons was constrained within the investigation by isolating specific temporal and spatial ROIs for the investigation. Specifically, significant area of interest in EEG Task 2 in Chapter 5 was identified based on a group of control infants (i.e. those with typical likelihood of ASD), and then only significant bands and areas of interest were subjected to a group analysis. This analysis approach was designed to constrain the number of contrasts made in testing effects of developmental outcome, in order to minimise Type 1 error and maximize power in this relatively modest sample. However, this approach was not used for analyses of EEG Tasks 1 and 3 due to exploratory nature of the investigation and high possibility of a Type 2 error if a single group was excluded from further analysis.

Lastly, single-trial phase values (ITC) were compared in the 10-20Hz range in EEG Task 2. Due to exploratory nature of ITC, no exact predictions were made as to the temporal ROI and regions of significant ROI are defined through visualisation of the group grand average. Note that ITC values have been observed as generally lower in infants than adults and therefore no strong predictions were made about these responses.

Within the majority of these analyses, analyses of co-variance (ANCOVAs) or linear mixed models (LMMs) will be used on the data, depending on the nature of the sample, carried out in SPSS (Version 23). ANCOVAs were used to compare differences between groups while controlling for influence of confounding variables (typically Sex, Age(days) or number of

trials). On the other hand, LMMs were used in repeated measures designs. LMMs are particularly useful in infant populations as they estimate for missing data and increase the overall power of analysis and are predominantly used in Chapters 3 and 4 (West, 2009).

2.6 From Neuron to Phenotype: Establishing Links Between Brain and Behaviour

One of the key challenges for developmental and neurophysiological studies has been producing neural and cognitive correlates of behaviour. This is particularly important in the context of the search for biomarkers for later atypical development and the emergence of developmental disorders such as ASD (Isler et al., 2012; Johnson, Jones, & Gliga, 2015; Rojas & Wilson, 2014; Walsh et al., 2011). A summary of developmental research by Johnson and colleagues (2015) suggested that there are several core domains where specific changes between 0-2 years of life can be observed in children with ASD or ADHD (Johnson, Gliga, et al., 2015). The researchers emphasised the influence of bidirectionality, which is an important concept in the original IS framework (Section 1.2.3; Johnson, 2000, 2011). One particular domain investigated in the present work is perception and sensory processing, and potential manifestations of atypical developmental pathways within this core module on later development. Previous investigations have associated early neural responses to sound to later language development (Benasich et al., 2008; Cantiani et al., 2016; Choudhury & Benasich, 2011) and ASD symptomology (Eigsti & Fein, 2013; Jones, Venema, Earl, Lowy, & Webb, 2017; Kolesnik et al., 2019; Young et al., 2009), although the evidence field is still relatively novel. In accordance to one of the main aims of this thesis, the following experimental chapters will also consider the relationships between key neural markers of age-dependent specialisation with observer ratings of infant cognitive ability (i.e. Mullen Scales of Early learning; Mullen, 1995; ASD severity scores in selected samples only; Gotham, Pickles, & Lord, 2009) as well as parent ratings of behaviour (i.e. temperament, language ability, and sensory sensitivity;

(Dunn & Daniels, 2002; Putnam, Helbig, Gartstein, Rothbart, & Leerkes, 2014; Thal et al., 2007). The present work will be evaluated based on the relationship between particular behavoiural, biological or cognitive markers and later development, within infants with and without familial or genetic likelihood of ASD/ADHD.

2.7 Pre-registration

Pre-registration is a recently developed open research practice, in which researchers are encouraged to submit the rationale, methodology and analytic strategy of their studies at either the beginning of data collection or prior to data analysis (Gonzalez & Cunningham, 2015). The proposal is then peer-reviewed in a similar way to a full manuscript submitted for publication, after which the study is approved in principle by the journal. The pre-registration was done to increase transparency in research and decrease publication of false positive results. This practice has somewhat been adapted within this thesis, and tasks described in Chapter 4 (Pre-registration doc 1: *Experience-dependent specialization of auditory processing in infancy and later language acquisition*) pre-registered internally on 23/06/2019. Internal pre-registration process is completed along the same guidelines provided by Open Science, and has been reviewed within the members of the department and testing team. After the document with planned hypotheses and analyses has been accepted by all contributing authors, a document was dated and sent to Professor E. Jones to hold until task analyses are complete. These documents will be included in Appendices for Chapters 4 and 6 respectively.

Chapter 3. Acquiring Expertise - Exploring Behavioural Markers of Infant Communication

The following chapter examined behavioural indices of communication and expertise towards the native language in typically-developing infants between 5 and 14 months of age. One way in which this can be achieved is by examining parental report of language skills, and several standardised metrics are available to assess pre-verbal communication abilities (Cates et al., 2012; Dreyer et al., 1996; Fenson et al., 2007). However, parent report has been critiqued as being too simplistic and indirect to relate to neural indices of language processing. The study of speech and language perception dramatically changed with the increasing use of eye tracking technology (see Chapter 2.1.1 for outline of visual behavioural techniques). Due to increased objectiveness of the technique as well as links between gaze patterns and underlying brain processes (Aslin, 2012), eye tracking became recognised as a more robust index of infant cognition. Further, the method can be used with participants of any age and has low attrition rates, which makes it highly useful when it comes to looking at longitudinal change in a skill or ability.

The tasks featured in this chapter include findings from eye tracking studies of active seeking of native or non-native language, matching audiovisual speech cues and scanning of talking faces in native and non-native languages. Speech perception is one of the main pillars of social communication and is thought to be constructed from both auditory and visual information, which further justifies the chosen methodology (Burnham, Campbell, & Dodd, 2013). The following chapter described data from typically developing infants only, as I explored whether eye tracking was a sensitive measure of specialisation. Specifically, robust age, language (i.e. differences in gaze/pupillary responses based on the language of the stimulus) and language experience effects are expected before addressing how these variables

may differ in individuals with atypical developmental trajectories. Results from the experiments described in this chapter were used to investigate relationships between gaze behaviour and electrophysiology (Chapter 4.5). Using a range of visual behavioural techniques provided the necessary additional phenotypic information that is not captured by neurophysiological measures nor observer/parent report on the child's abilities. It should be noted that alternative techniques are available to study early language perception (i.e. EEG), which are featured in the Chapters 4-6 of this work.

Expertise is defined here as the increase in ability between infancy and early childhood to comprehend and communicate using a native rather than a non-native or non-speech sounds. Specialisation refers to the underlying changes in the brain which facilitate development of cognitive, motoric and behavioural competencies (Johnson, 2011), specifically in relation to social brain networks. Establishing links with neurophysiological markers may help better understand the relationship between brain responses to incoming information and behaviour, which is necessary for advancement of speech perception literature. See Chapter 1 for detailed explanation on why communication (i.e. speech perception, social attention) was selected as a domain in which to study of experience-dependent specialisation.

As previously stated, infant communication develops from crying, to cooing and babbling ('ba-ba', 'ga-ga'), and culminates in production of their first words around 10-18 months of age in infant's native language. Recent decades have seen numerous studies focusing on specific neural mechanisms which facilitate specialisation towards early stages of language acquisition, including narrowing of phonetic discrimination (Grieser & Kuhl, 1988; Mann, 1986; Maurer & Werker, 2014; Werker, 1989) and increased preference towards the native language between birth and 10 months (Kuhl et al., 2006; May, Byers-Heinlein, Gervain, & Werker, 2011; Moon, Cooper, & Fifer, 1993). It is argued that, in addition to biological and experiential factors, age-dependent increase in specialisation may be a mechanism that guides

phonological development (Werker & Tees, 2005). Comprehension and acquisition of speech is complex, and does not only rely on sounds information only, which weakens the ecological validity of many of the previous studies. In order to fully explore the links between behaviour and early neural specialisation, more accurate representations of speech perception and acquisition are required, i.e. by studying how infants react and attend to social situations – where learning actually takes place. This is addressed by the three tasks described in this chapter.

Gaining expertise in social communication and language may be affected by the number of languages that the infant hears in their daily environment. Due to the multicultural setting of the present investigation, previous experience with two or more languages was explored as a possible factor underlying individual differences in infant's cognitive and behavioural abilities. Literature suggests that exposure to non-native stimuli maintained responsiveness beyond the age typically associated with narrowing, both from short term exposure in experimental settings (Kuhl, Tsao, & Liu, 2003; Pons, Lewkowicz, Soto-Faraco, & Sebastián-Gallés, 2009) as well as exposure to two or more languages in the home (Byers-Heinlein & Fennell, 2014; Werker, 2012). The implications of exposure to multiple languages and cultural backgrounds in early life has captured the interest of many developmental researchers, as some reported increased domain-general cognitive flexibility (Adesope et al., 2010; Adi-Japha et al., 2010; Kuipers & Thierry, 2013), while others noted potential delays in linguistic milestones relative to peers exposed to a single language (Petitto & Holowka, 2002). Thus, there is reason to believe that there are differences in the trajectory of communication abilities, and ergo specialisation of the social brain, in infants with additional language experience relative to those in single-language homes.

The following sections outline results from one group of infants, who came into the lab to take part in a longitudinal study. The first task looked at how infants' active seeking of

language input changes in the first year of life *(*Task 1). The second task looked at how infants learn to match and predict audiovisual speech cues (Task 2). And lastly, age-related changes in attention towards the eyes and mouth were studied through a selective attention paradigm (Task 3).

Defining experience-driven specialisation in this chapter involved three distinct stages. Firstly, I looked at how looking behaviour changes over developmental time as well as between infants with different levels of language experience. Then, stability of these measures was assessed over developmental time within each individual (i.e. is performance on certain tasks consistent between different age points). Lastly, I explored how these eye tracking indices may relate to standardised behavioural scores, and whether they are associated with standardised measures of communication ability. These analyses were repeated for all three tasks within this chapter.

3.1 Eye tracking Task 1: Active Seeking of Language Input

This experiment has been included the in manuscript *'Active seeking of native language increases and is shaped by language experience in pre-verbal infants'*, which is currently in preparation for submission.

The following experiment was designed to examine if and how infants seek out their native language from their environment. Measuring language seeking attempts to capture the bidirectional relationship between the infant and their environment, where the viewer is able to choose and regulate the incoming stream of information. This aspect is particularly important to assess in the context of existent literature that is largely based on passive viewing paradigms or proxy measures of preference such as head turning or sucking behaviours. Firstly, present knowledge of pre-verbal communication and language skills was considered. The 'passive viewing' methods prevalent to existent literature were then evaluated in comparison to an

'active' search paradigm that can be used to capture infant interaction with their linguistic environment. Measuring active seeking rather than passive viewing behaviour is an important first step in measuring infant specialisation towards their native language and pre-verbal communication, as observation of age-dependent changes will be more representative of infant learning in their natural environment.

It has been reported that neonates show recognition or preference of human speech sounds, including their mother's voice (DeCasper & Fifer, 1980), song (Whaling et al., 1997) and general speech in their 'native language' from an unfamiliar speaker from as early as 2 days after birth (Moon et al., 1993). The early selective attention to speech has been attributed by nativist theorists to an innate adaptive ability that occurs at pre-specified times during early life (Chomsky, 1986, 1998). It is thought to be guided by early experience with a 'native tongue', which thereafter constrains language acquisition (Kuhl & Meltzoff, 1997). Learning theorists, on the other hand, argue that this selectivity is due to the small amount of experience (i.e. days or weeks) that the infant receives before being engaged in the experimental task. More convincing evidence has emerged, which argues that prenatal auditory experience in the womb affects pre and post-natal responses to the mother's voice (Kisilevsky et al., 2003; May et al., 2011). Researchers suggested that while neonates display an arbitrary preference towards familiar speech stimuli, their sensitivity is much broader than that of a child or adult. It is through the course of developmental time that they are able to streamline their sensitivity in line with increasing exposure to social stimuli.

3.1.1 Specialisation through perceptual narrowing towards the native language.

Research into early speech perception revealed that the increased sensitivity and responsiveness to non-native languages, faces, vocalisations, and music decline between infancy and childhood in a process termed perceptual narrowing (Maurer & Werker, 2014; see Chapter 1.4.3). This phenomenon is particularly relevant to the study of specialisation, as the

decrease in responses to non-native stimuli is assumed to index an increase in language proficiency over developmental time. Perceptual narrowing a striking concept within developmental psychology, where cognitive and perceptual skills are perceived to be incrementally increasing. It has been reported that infants are initially able to discriminate between sounds found in many different languages (Eimas, Siqueland, Jusczyk, & Vigorito, 1971; Streeter, 1976). The 'universal listener' capacity diminishes with increasing experience with a native language by the second half of the first year (Eimas, 1985; Gervain & Mehler, 2010) and is no longer present by adulthood (Best, McRoberts, & Goodell, 2001; Zhang, Kuhl, Imada, Kotani, & Tohkura, 2005). Simultaneously, there is an increase in the infants' ability to perceive phonetic contrasts in their native language (Kuhl et al., 2006). There is a measurable decrease in sensitivity to differences not present in the native linguistic and social environment.

It must be recognised that narrowing is not a loss of perceptual capacity, but simply a 'tuning' or specialisation of perceptual mechanisms based on experience, which leads to a decrease in sensitivity to non-native information. There are several models which specifically consider the mechanistic foundation behind perceptual narrowing and speech perception development which are beyond the scope of this chapter (reviews by Aslin & Pisoni, 1980; Gottlieb, Oudeyer, Lopes, & Baranes, 2013; Maurer & Werker, 2014 cover this topic). Nonetheless, large gaps remain in the understanding of the how selective attention and preference towards speech sounds are related to language learning. This is in part due to emphasis of experimental paradigms on passive or age-constrained observational techniques as well as the use of cross-sectional designs.

Several researchers reinforced the idea of 'critical periods' in development (Bailey, 2001; Werker & Tees, 2005), and argued that attainment of pre-verbal language/communication milestones are predictive of later language outcomes. Using predictions set out by the Interactive Specialisation framework (IS, Chapter 1; (Johnson, 2011)

recent studies showed that age-related changes in attentional focus result in increased expertise towards the native language between early infancy and childhood. It is widely accepted that increased attention facilitates information processing and encoding (Campbell, Hayne, & Richardson, 2014) while a decrease is detrimental to these processes (Craik, Govoni, Naveh-Benjamin, & Anderson, 1996; Klingberg, Forssberg, & Westerberg, 2002).

One ability in particular, the increase of orienting towards a speaker of a native language, is thought to reflect a common mechanism of information seeking (Begus, Gliga, & Southgate, 2016). A recent study found that infants consistently ignored the foreign speaker and attended to the native speaker. This selectivity was supplemented by increased EEG-oscillatory activity in the theta band, which is associated with active and selective preparation for information encoding in adults (Fell et al., 2011). It was concluded that preference for native speakers may be an adaptive mechanism used to facilitate learning. Literature on toddler language preference revealed that they are more likely to pay attention to speakers of their native language, as well as interpret the actions of those speakers as more reliable than those of accented speakers (Kinzler, Corriveau, & Harris, 2011) or foreign language speakers (Soley & Sebastián-Gallés, 2015). It should also be noted that perceptual narrowing occurs over multiple domains (i.e. visual; Pons, Lewkowicz, Soto-Faraco, & Sebastián-Gallés, 2009). The findings above support the Interactive Specialisation framework, as specialisation of intercessory perception is practically inconceivable in the absence of social interaction.

3.1.2 Limitations of infant 'preference' studies.

Previous literature in the field has relied on a set of experimental paradigms to examine infant's behaviour (including High Amplitude Sucking, Conditional Head Turning and Visual Habituation Methods), which are not likely to resemble language learning in a naturalistic environment. Additionally, these studies do not reflect the mechanisms behind infant preference for familiar object/faces (Colombo & Mitchell, 2009; Houston- Price & Nakai,

2004). Due to this, there some studies report attrition rates in such task designs as infants fail to habituate (where participants are selected to perform the main task based on their performance on a discrimination task) or stay still during the procedure; although many variations exist to address these limitations i.e. by using an added visual dimension to engage participants (Burnham & Dodd, 2004; Mcgurk & Macdonald, 1976; Patterson & Werker, 1999). What's more, passive experimental designs such as looking time paradigms may not sufficiently reflect 'preference' or understanding. For example, Keen (2003) found that 2-year-olds were not able to perform a task where they had to find a hidden object (by making an overt action), which is in contrast to a series of studies that concluded that 3-month-olds were able to perform the task based on higher looking times to the 'correct' visual scene.

Moreover, infant gaze behaviour is typically measured relative to stimuli presented on the screen, which is not representative of social interaction in everyday life. I addressed this limitation in the task below, using predictions set out by the Perceptual Narrowing and the IS framework, to explore how 'active seeking' of linguistic input changes between 5 and 14 months, as well as how exposure to more than one language may affect this trajectory.

3.1.3 Present study.

In this task infants were shown two videos successively with either English or Italian infant-directed phrases on either side of the screen (Practice Trials), after which a saccade to either side of the screen would initiate a video in the corresponding language (Test Trials). The purpose of the Active Seeking task was to observe developmental changes (between 5, 10 and 14 months) in seeking of language input with increasing experience with a native language in the first year of life. Fourteen infants in the sample were reported to have at least 30% exposure to additional languages and made up the Additional Language Exposure (ALE) subgroup. This is a small group with varying amounts of non-English (nor Italian) input and is therefore used only as proof of principle that this paradigm is sensitive to individual differences. Primarily,

an age-dependent increase is expected in basic metrics of gaze and pupil dilation between 5, 10 and 14 month groups. Based on current literature, I predicted increasing preferences towards the infants' native (English) versus non-native (Italian) language, reflected by greater proportion of choice, faster reaction times, greater looking time and larger pupil dilation between 5 and 14 months. This developmental change was expected to be modulated by language experience received by the child. Specifically, infants with additional language experience were expected to show an increased preference for the non-native language stimuli.

3.2 Methods

3.2.1 Participants[10].

Fifty-two infants (25 males, 27 females) were recruited to take part in the study. All participants were born at full term (gestational ages 38-42 weeks), with their families contacted through a volunteer database at the Centre for Brain and Cognitive Development (CBCD) at Birkbeck, University of London. Families attended three visits, at 5 (*n*= 48, *M*=5mo15d, *SD*= 9.5d), 10 (*n*=48, *M*=10mo6d, *SD*=8.12d), and 14 (*n*=39, *M*=14mo22d, *SD*=14d) months, with 38 families completing all three visits (see Table 3.1 and 3.2 for descriptive statistics of the sample). Parents reported no family history of developmental disorders nor any issues with vision or hearing, based on interviews carried out during the first visit. Fewer infants attended the 14-month visit due to 2 families emigrating, 5 families having additional children and not being able to travel and 4 unable to attend the last experimental visit due to other commitments. To be included in the study, infants had to hear English in the home at least 30% of the time,

[10] The group of participants discussed here will also be featured in the two eye tracking tasks described below as well as the EEG data from typically developing controls discussed in *Chapter 4*.

and were classified as having additional language exposure if they heard at least 30% of another language in the home (ALE subgroup, n=14). Infants' language exposure was measured by a Language experience interview during the 5-month visit (Appendix B). Another important criterion was that none of the children were exposed to Italian or Dutch in their home, as it would interfere with the 'novelty' of the non-native language stimuli presented in eye tracking Tasks 1 and 3. One infant in the sample received <5% English input between visits 1 and 2 and was therefore excluded from analysis. Out of the children who attended, six did not provide eye tracking data at Visit 1 due to difficulties in achieving calibration or tiredness, all infants who attended Visits 2 and 3 provided adequate data for analysis. Note that during the last visit (14 months), fewer datasets were available relative to the other groups (Table 3.3), which was due to measurement error during recording (n=2) or tiredness of the infant (n=9).

Table 3.1 *Descriptive statistics of the sample: sex, % language input mean, range; age, raw scores on the Expressive and Receptive Language scales on the MSEL (Mean, SD).*

	Total Sample	**English-only**	**ALE**
Sex (m,f)	24m, 28f	15m, 23f	9m, 5f
% English heard input (M, range)		*M*=98.3%, 80-100%	*M*= 50%, 30-70%
5 months			
Age in months (SD)	5.5 (9.5)	5.5 (9.23)	5.4 (10.16)
MSEL Receptive Language	4.7 (1.45)	4.8 (1.53)	4.42 (1.24)
MSEL Expressive Language	5.91 (.9)	6.06 (.96)	5.5 (.52)
10 months			
Age in months (SD)	10.4 (8.12)	10.45 (8.6)	10.36 (5.8)
MSEL Receptive Language	8.67 (2.12)	8.92 (2.19)	7.8 (1.68)
MSEL Expressive Language	8.45 (1.78)	8.64 (1.62)	7.8 (2.04)
14 months			
Age in months (SD)	14.7 (15.3)	14.7 (16.5)	14.5 (7.98)
MSEL Receptive Language	13.54 (2.5)	13.71 (2.53)	13 (2.44)
MSEL Expressive Language	13.65 (3.83)	13.96 (3.73)	12.67 (4.18)

Table 3.2 *Maternal education across groups.*

Maternal education (%)					
Group	Primary	Secondary	Tertiary Undergraduate	Tertiary Postgraduate	Declined to Answer
English-only	0%	12.1%	27.3%	60.6%	0%
ALE	0%	7.7%	7.7%	76.9%	7.7%

Note. The groups were broadly comparable in the maternal education of families enrolled in the GABBLES study. A chi-squared test of the number of parents with secondary vs. tertiary undergraduate vs. tertiary postgraduate did not reveal significant differences between language experience groups ($\chi 2$=4.73, p=.192). Generally, the table suggests that most parents had high levels of education. Socio-economic status has been operationalised as maternal education is commonly used in the US as well as in a recently published European infant study (Jones et al., 2019). Access to higher education is comparable for this sample as families have been recruited from in and around London, UK.

3.2.2. Stimuli and apparatus.

The stimuli used for the Active Seeking task were a series of infant directed phrases recorded at 25 frames per second as part of a larger battery of eye tracking measures. All videos were recorded on site of CBCD, in which the female Italian-English bilingual speaker produced phrases in either native or non-native languages (i.e. English: “Good Baby!”, “Keep Looking!”; Italian: “Bravo Bambino!”, “Buon Lavoro!”; Figure 3.1). The videos in the test trials were presented as stills side-by-side on the screen, until a saccade was made after which, the video on the chosen side played. Each language had an allocated side of the screen (English – Right, Italian – Left, see Figure 3.1), and the location was counterbalanced in the two repetitions of the task. The background was light purple (RGB 204 204 255) and no videos contained objects or examples of social interaction such as hand movements or gaze following. Infants were

encouraged to fixate in the centre of the screen with an attention-grabber (i.e. a simple image of a cartoon flower in the centre of the screen, animated until gaze falls upon it).

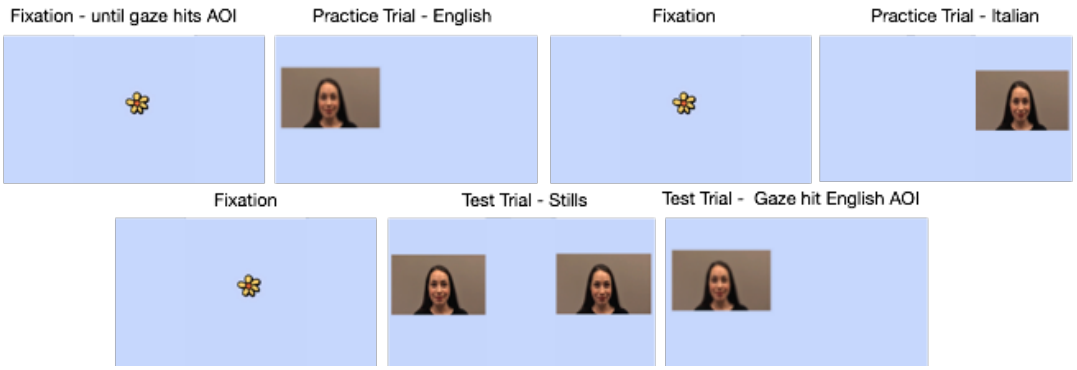

Figure 3.1 The trials consisted of videos of simple infant-oriented baby phases in English and Italian. From left to right – Initial presentation of English and then Italian phase on either side, fixation screen, video stills presented on two sides where infant must make a saccade to either AOI to trigger the play the next video.

Video stimuli were presented using an in-house Matlab script which called functions from Psychophysics Toolbox (Kleiner et al., 2007) to display videos on the screen of a Tobii TX-300 eye tracker (diagonal width: 23", screen resolution: 1920x1080). Raw eye tracking data were acquired at 120Hz by the TX-300, via the Talk2Tobii toolbox (Deligianni, 2007) from which the data were saved to an external disk. Each frame of video was time-stamped relative to the clock on the eye tracker, so that any individual frame of video could be aligned with a particular sample of eye tracking data (See Data Analysis). Videos were presented for an average of 5.5 seconds with a 1 second inter-trial interval.

3.2.3 Procedure[11].

Infants were sat on the parent's lap 1 meter from the eye tracker (visual angle of the stimulus 112° 37' 0.19"; based on average distance from the screen) and watched a clip from an animated children's programme while I adjusted the position of the tracker to ensure that the infant's eyes were detected. I instructed the parents to close their eyes during this part to ensure that the tracker was not picking up their eyes instead. Once the tracker was appropriately positioned, I would go behind a curtain and out of sight of the infant.

Then, an automatic five-point calibration sequence was started. If fewer than 3 or 4 out of 5 calibration points were acquired, calibration was considered poor, and the sequence was run again in an attempt to improve data quality. If the calibration was not successful after 5 attempts, the participants were not able to take part in this part of the study. This judgement was based on the individual infant and parents, i.e. would they have tolerance for repeated calibration without losing interest in the screen. The entire task battery lasted 25 minutes, broken into two 10 and 15 minute parts, between which infants and parents were encouraged to take a short break.

For the Active Seeking task, infants were initially presented with two consecutive Practice Trials. The first trial started with a video on one side of the screen (e.g. right side – English phrase) followed by the second trial with a video in another language on opposite side (e.g. left side – Italian phrase). From the third trial, the Test Trials commenced with presentation of the fixation image, during which the eye tracker verified that the infant attended

[11] Identical experimental procedure was employed for all three tasks in this chapter, as they were administered in an eye tracking battery.

to the fixation before presentation of two video stills on either side of the screen. Once the gaze reached either the right/left AOI the video on that side would play, with the other still disappearing from the screen. Excluding the two demonstration trials, there were 10 Test Trials in Part 1 of the battery, and 8 Test Trials in Part 2, where the language sides were interchanged. If infant became distracted, the experimenter used a noise-making toy out of sight to attract their attention back to the screen.

3.2.4. Data reduction and cleaning.

Raw eye-gaze data for both parts of the session was segmented into epochs around each stimulus video (i.e. trial). Gaps in the data of less than 150ms were linearly interpolated. When both eyes were detected by the eye tracker, the x and y coordinates from both eyes were averaged to make single x and y coordinates. If only one eye was detected, only x and y coordinates of the detected eye were used.

All cleaning procedures were performed in R Studio (Version 1.1.383; (RStudio, 2012)) collapsed across participants and age points. Note that conservative data cleaning methods were used in this analysis to reduce the possibility of noise in the data interfering with the active choice paradigm (relative to Task 2 and 3, which used more traditional passive viewing metrics). Each trial from the active seeking task was considered valid if (a) reaction time for initial saccade was in the .25 -.75 quartile range collapsed across Age Point and Task Part, and (b) percentage of data samples lost (i.e. when eyes were not visible) was less than 30% of the total samples acquired during the session[12]. Following this, only datasets where more than 25%

[12] Percentage of valid data for this task is a more conservative value of data samples relative to 50% used in eye tracking Tasks 2 and 3 featured in this chapter. This was done to reduce the possible effects of noise due to the exploratory nature of the task.

of the total trials remained valid were retained for further analysis. These conservative measures were taken in order to reduce the impact of noise and confounding variables on the data. Proportional looking time variable was further corrected, excluding fixations made to the opposite side to where the initial saccade was made. For details of datasets kept after the three rounds of the cleaning procedure see Table 3.3. Note that overall there were fewer valid trials in Part 2 due to tiredness and loss of concentration from the infants, although no differences in looking times or preference towards left or right side of the screen were revealed (all *p*s >.1). Therefore, datasets were collapsed across parts 1 and 2. After cleaning, data was imported into SPSS (IBM, V23) for statistical analysis.

Table 3.3 *Sample size retained for gaze analysis following data cleaning steps*

Age Point (N data/visits)	*RT correction*	*AOI samples correction*	*Number of Trials above 25 percent*	*Overall retention rate*
***5m** (41/45)*	40.5	40.5	27.5	67%
***10m** (44/48)*	41	41	37	90%
***14m** (28/39)*	24.5	24.5	21	85%

Note. Differences in sample size at 14 months are explained in Chapter 3.2.1. *RT correction* = to be included the initial saccade had to be in the .25 -.75 quartile range collapsed across Age Point and Task Part; *AOI samples correction* = the samples acquired had to have data loss of less than 30% of looking towards the stimulus to be included in the final analysis.

3.2.5 Gaze data analysis.

There were three main dependent variables calculated from this task: Proportion of Language Chosen (PropChosen), Reaction Time (RT) and Looking Time (LT). PropChosen was the total count of saccades made towards English Stimulus at the start of each trial over the total number of trials, where at least one saccade had to be made towards one of the two

AOIs. RT was the time between start of trial (fixation point and two videos side by side) and when gaze hit either AOI, measured in milliseconds. Lastly, LT was defined as a proportional looking time to an AOI after the initial saccade (i.e. relative to the total looking time of that trial). Two different analysis techniques were used to compare differences in performance across age and language groups, with alpha level at 0.05 and confidence intervals (CI) reported as estimates of effect size. Post hoc tests for significant interaction terms were carried out using pairwise comparisons of estimated marginal means using Sidak adjustment to account for multiple comparisons (West, 2009).

For the analysis of the selected dependent variables, separate linear mixed models were used, as these measures were unbounded continuous variables and thus require a normal error estimation (Warton & Hui, 2011). The models were initially carried out on the total sample, irrespective of language input (Model 1 and 3), followed by a second model, with inclusion of Language Experience as a fixed factor and interaction term where applicable (Model 2 and 4). As Proportion of English versus Italian adds up to 1, only PropChosen for English videos only was selected as a dependent variable in the models below:

PropChosen ~ AgePoint + trial number + sex +(AgePoint1| ParticipantID); [1]

PropChosen/RT/ LT ~ AgePoint * LanguageExperience + trial number + sex + (AgePoint1| ParticipantID); [2]

The model was adjusted for the following two dependent variables, which includes a comparison of reaction and looking time towards either English or Italian stimuli:

RT/ LT ~ AgePoint * Stimulus + trial number + sex +(AgePoint 1| ParticipantID); [3]

RT/ LT ~ AgePoint * Stimulus * LanguageExperience + trial number+ sex + (AgePoint 1| ParticipantID); [4]

Where RT/LT was the dependent variable and the model terms to the right, including "AgePoint" (5,10, 14 months), and "Stimulus" (English, Italian) as fixed factors, gender and trial number as covariates, with a random intercept only term "1| ParticipantID", (Model [1]). For this analysis, interactions were allowed for Age Point, Stimulus and main effects of covariates were examined. Random intercepts and slopes were allowed for each participant within Age Point. Results (estimate of the coefficients, standard error, degrees of freedom, t and p-values (alpha level .05) and 2.5 - 97.5% confidence intervals) are reported in the next section.

3.2.6 Pupil diameter analysis.

Pupil size was measured continuously through the task and aggregated into 6 second blocks from the onset of each trial. Several steps were taken to reduce the noise in the raw data, following existent reports on infant pupil diameter (Hepach & Westermann, 2016; Hoehl, Hellmer, Johansson, & Gredebäck, 2017). First, trials with the number of samples with low pupil data quality (validity = 4 from both eyes) in more than 50% of the total looking time were excluded. Pupil diameter was then averaged between two eyes if at least one eye was present. A correction was applied for individual rate of change, and data points excluded if they were above or below the upper and lower bounds of the interquartile range (which was calculated individually per participant, part and trial; see Table 3.2 for pupil analysis sample size and preserved data points). The deleted data points were replaced through interpolation, as described below. No significant differences were found in PD between Parts 1 and 2, so they were collapsed for further analysis.

The participants contributed with an average of 8.03 (*SD* = 1.85) trials at 5 months, 8.32 (*SD* = 1.76) trials at 10 months, and 8.62 (*SD* = 1.43) at 14 months. Linear interpolation was applied to the data for a maximum gap of 5 samples, which is common practice in the field. Following interpolation, 95.69% of the available data was retained for further analysis. A moving average filter was then applied to the data (backward window length = 5). After this, the data was transformed using a smoothing spline function. As pupil size varied between participants and trials, a baseline correction was applied using a correction factor (i.e. 100ms from the start of the trial were averaged and then subtracted individual pupil diameter estimates (Hoehl et al., 2017)). The analysis interval was defined as 2.5-3.5 seconds from stimulus onset, based on previous investigations in infant pupillary responses where effects were visible from 2 seconds (Hoehl et al., 2017; Sirois & Jackson, 2012).

Table 3.4 *Sample size retained for pupil analysis. Original sample denotes the number of datasets acquired from each visit. Pupil Dilation final sample is the number of datasets that remain following lost data and minimum number of trials correction. Part 1 and 2 denote order of administration of the task.*

Age Point (N data/visits)	*Original sample*		*PD final sample*		*% Preserved data*	
Part	*1*	*2*	*1*	*2*	*1*	*2*
5m (41/45)	41	41	41	39	97.76	97.72
10m (44/48)	44	38	41	35	97.72	98.44
14m (28/28)	28	21	28	21	97.79	98.54

Baseline corrected pupil diameter (PD) was averaged over the chosen time window for each infant, with an additional Stimulus language factor which denoted the direction of the first

saccade (i.e. English vs. Italian). Statistical analyses were performed in SPSS using a mixed model with the following terms:

PD ~ sex * AgePoint * Stimulus +trial number +sex +(AgePoint | ParticipantID); [5]

PC ~ sex * AgePoint * Stimulus * LanguageExperience +trial number +sex + (AgePoint | ParticipantID); [6]

PD as a dependent variable with Sex, Age Point, Stimulus as fixed predictors, varying random slopes and intercepts for each participant within an Age-Point. The model included an interaction between Age Point and Stimulus Language. A second model was run with Language Experience (English-only vs. ALE) as an additional fixed factor and interaction term.

3.2.7 Behavioural analysis.

Lastly, performance on the active seeking task (i.e. taken separately from Prop Chosen, Reaction Time, Looking Time and Pupil Diameter) was correlated with individual levels of language development measured through standardised parent and observer reports using Pearson's Product Moment Correlation Coefficient. This included raw scores on the Expressive (EL) and Receptive Language (RL) subscales on the Mullen Scales of Early Learning (Mullen, 1995) at 5, 10 and 14 months, as well as vocabulary size (defined by number of words that the child (1) Understands and (2) Understands and Says) on the MacArthur Bates Communicative Development Inventory Words and Gestures (CDI-WG, Fenson et al., 2007) at the 14-month visit (CDI scores from 5 and 10-month Age Points and were not included, due to possible limitations of this measure before the age of 1; Feldman et al., 2000).

3.3 Results

3.3.1 Gaze analysis.

The active seeking task was administered in two parts of a large eye tracking battery. There were no significant effects of Part on English PropChosen ($F(1,41)=.0025$, $p=.87$, $\eta_p^2=.0001$), RT ($F(1,34)=0.172$, $p=.68$, $\eta_p^2=.0002$) or LT ($F(1,34)=-0.018$, $p=.89$, $\eta_p^2=.0001$) variables. Therefore, trials were collapsed across Part for all further analyses. Sex and Trial number were accounted for as additional covariates to the original models.

3.3.1.1 Stimulus Choice.

Firstly, preference for either native versus non-native stimuli were examined against chance level (50%) at each Age Point in analysis. The one-sample t-test split by Age Point did not reveal significant differences between the proportion of language chosen at 5 ($p=.89$), 10 ($p=.81$) or 14 ($p=.36$) months. To look at 'preference' towards the native English stimuli videos, the proportion of English videos chosen was entered into a LMM dependent variable with all participants irrespective of language experience. There were no effects of Age Point on the proportion of English chosen ($p=.647$), which remained non-significant when the number of trials and sex were taken into account. Adding Language Experience to the model [Model 2] did not show significant main effects or interaction terms (ps between .85-.76).

3.3.1.2 Choice Reaction Time (RT).

Two linear mixed models were carried out to examine differences in RT (with and without language experience as an additional fixed factor). The first analysis [Model 3] found an overall main effect of Age Point ($F(1302)=71.49$, $p<.001$, $\eta_p^2=.052$). Fixed effects analysis intercept for the 5 month group was significantly higher than that of the 10 months ($t(1296)=6.9$, $p<.001$, [*CI* 42.63 76.26]), i.e. slower RT in the younger Age Point, with no difference between 10 and 14 month-olds. There was no main effect of Stimulus language

(p=.36), and no significant effect of covariates Sex (*Wald Z*=.842, p=.4) and Trial number (*Wald Z*=.056, p=.95). When language experience was added to the model [Model 4], the main effect of Age Point remained, as well as a Age Point x Language Experience interaction (F(1296)= 9.63, p<.001, η_p^2=.014). Follow up simple effects analysis showed faster RT in English-only versus ALE infants at 5 months only (*Mean Diff*=-36.29, *df*=68.54, p=.016, *CI*[-65.71 -6.87]; Figure 3.2A). There was no main effect of AOI or interaction terms of interest. Covariates were not significant for Sex (*Wald Z* = .77, p=.442) or Trial Number (*Wald Z*= .524, p=.601).

3.3.1.3 Looking time to selected stimulus (LT).

In the LT model [Model 3], there was a significant effect of Stimulus (F(1352.85)=9.84, p=.002, η_p^2=.007). Mean comparisons showed elevated looking time towards Italian stimuli for all groups. The main effect of Age Point was not significant (p=.302, η_p^2=.0001) and covariate effects were not significant for Sex (*Wald Z*=.699, p=.485) or Trial number (*Wald Z*=.199, p=.485). With Language Experience added as a fixed predictor, the effect of Stimulus remained significant, with an added main effect of Age Point (F(162.17)=3.43, p=.034, η_p^2=.02), and interactions between Age Point x Language Experience (F(162)=3.58, p=.030, η_p^2=.042). Simple effects follow-up analyses showed that this effect was driven by lower looking time to the English stimulus in infants with ALE (*Mean Diff*=-.112, *df*=455.71, p<.001, *CI*[-.162 -.063]), while no Age Point or Language Experience differences were observed for Italian. Figure 3.2B shows some age differences in looking time towards the English stimulus, they failed to reach significance in the model. Covariates of Sex (*Wald Z*= 1.5, p=.113) and Trial number (*Wald Z*=-1.5, p=.110) were not significant.

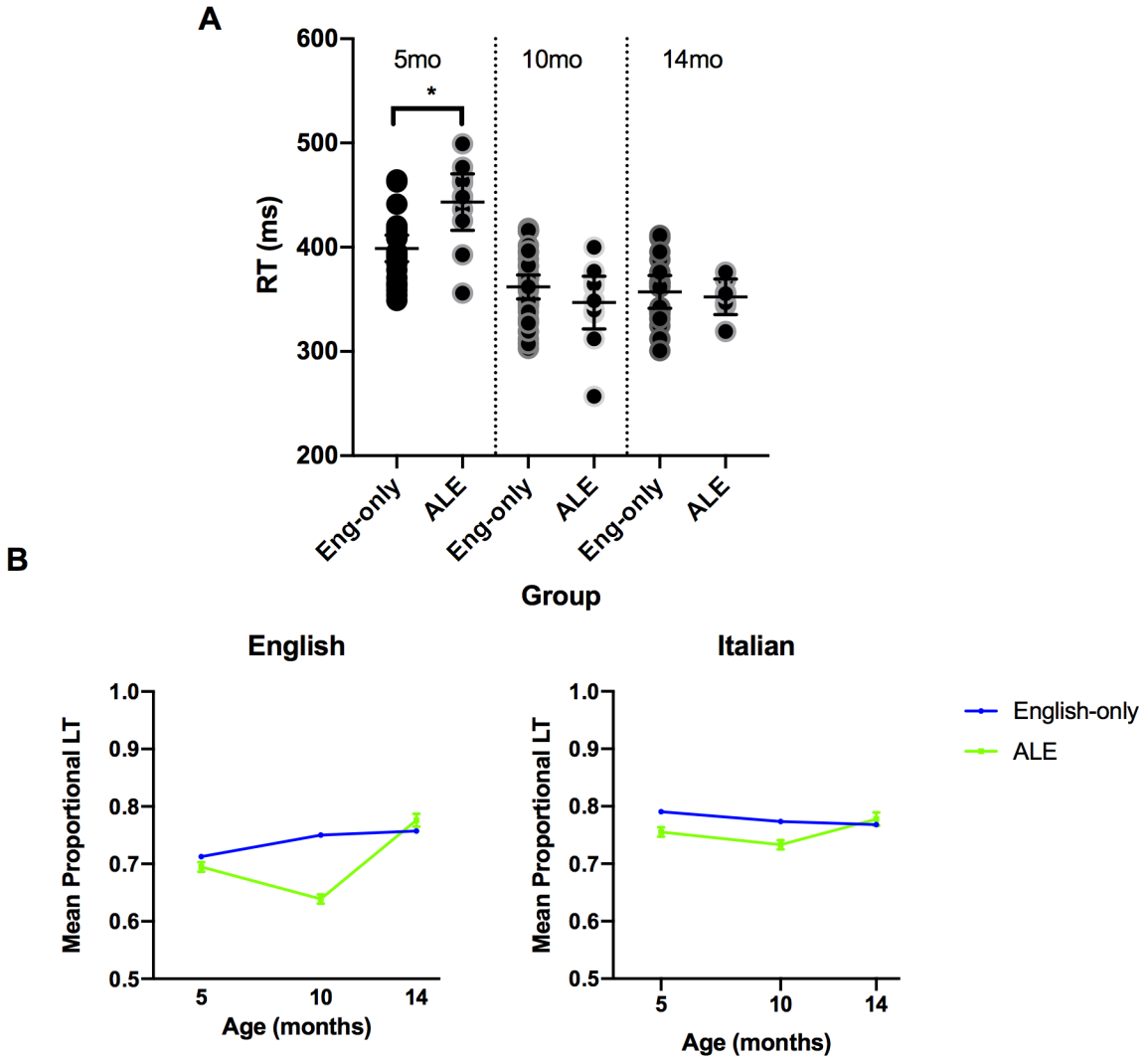

Figure 3.2 Plots demonstrating **(A)** Reaction Time in English-only and ALE groups across English and Italian Stimulus and **(B)** Line plots demonstrating change in LT across Age Points in English-only and ALE infants for English (left) and Italian (right) stimulus languages.

Note. **p*<.05, ***p*<.001. Black bracket denotes group and error bars show SE (95%). Estimated marginal means are visualised.

3.3.2 Pupil dilation analysis.

A LMM was carried out to assess variation in pupil diameter in the active seeking task. The overall model [Model 5], returned a significant effect of Age Point (F(879)=118.503, p<.001, η_p^2=.118, Figure 3.3A-B). Pairwise comparisons showed that PD was significantly lower in the 5 than the 10 (*Mean Diff=-.209*, *df*=880, p<.001, *CI*[-.244 -.173]) and 14-month groups (*Mean Diff=-.224, df*=880.9, p<.001, *CI*[-.265 -.184]), but no differences were reported between 10 and 14 month-olds (p=.651), showing developmental change over the first year of life. There were also no significant differences in pupil dilation between English and Italian stimuli. These effects remained with covariates added to the model, and effects of both Trial number (*Wald Z*=-1.57, p=.115) nor Sex (*Wald Z*=.263, p=.814) were not significant in the model.

With Language Experience added to the model, the effect of Age Point remained significant, with an added main effect of Language Experience (F(56.74)=4.07, p=.048, η_p^2=.067) and no effect of Stimulus language (p=.228, η_p^2=.0001). There was a significant three-way Age Point x Stimulus x Language Experience (F(879)=3.13, p=.0.44, η_p^2=.) interaction as well as an Age Point x Stimulus (F(875.7)=5.57, p=.004), Age Point x Language Experience (F(673)=22.73, p<.001, η_p^2=.009) and Stimulus x Language Experience (F(803.9)=8.65, p=.003, η_p^2=.021) interactions. As can be seen in Figure 3.3C, the increase of PD with Age Point is modulated by Language Experience depended on the language of the stimulus. Follow up simple effects analysis split by AOI with Sidak adjustment revealed significantly higher PD in ALE than English-only infants to English stimuli (*Mean Diff=.132,* p<.001, *CI*[.087 .178]), but not towards Italian (p=.103, η_p^2=.0002). Specifically, these differences appeared strongest (i.e. higher PD in ALE than English-only group) at 10 (F(1,404)=18.66, p<.001, η_p^2=.044) and 14 months (F(1,404)=38.68, p<.001, η_p^2=.087) for English and at 14 months (F(1,471)=9.83, p=.002, η_p^2=.024) for Italian stimuli.

3.4 Stability of Individual Differences Over Time

Next, stability of individual gaze and pupil diameter changes were examined over time. This was done through a series of correlation analyses between individual averages between 5 and 10 months, and then between 10 and 14-month Age Points. Due to normal distribution of gaze and pupil dilation data within the sample, parametric Pearson correlation coefficient was used in the present analysis. For reaction and looking time comparisons, partial correlations were used, controlling for Stimulus language (English vs. Italian).

For Prop English Chosen, there were no significant associations between number of English videos chosen between individuals across all Age Points (r -.038-.199; p .51-.86), which suggested that there is no relationship between active choice of native language within each individual participant across age. There was a significant positive association between RT at 5 and 10 months ($r(54)=.364$, $p=.007$, CI[0.11 0.57]). When separated by Stimulus language, quicker reaction times to Italian at 5 months were related to quicker reaction time at 10 months of age ($r(29)=.414$, $p=.026$, CI[0.06 0.67]). For Looking Time, there were no significant correlations with Age Point, with or without partialling out for Stimulus language (r -.103-.207; p .59-.15).

Lastly, the stability of the pupil dilation responses during the active seeking task were investigated. No significant correlations were found between metrics of gaze and pupil dilation with behavioural scores. A partial correlation model separated by Age Point and Stimulus language revealed a significant positive association for PD between 10 and 14 months, showing an increase in individual pupil dilation English stimulus only ($r(18)=.478$, $p=.045$, CI[0.03 0.76]), which is consistent with the age-comparison data discussed above. Based on this analysis, differences in PD between Language Experience groups were investigated further. It was found that there were also positive associations between pupil size at 5 and 10 ($r(11)=.791$,

p=.004, *CI*[0.39 0.93]) and 5 and 14 months (*r*(7)=.857, *p*=.014, *CI*[0.38 0.97]), but only in ALE group. It should be noted that sample sizes were much lower in the ALE group and findings from this group must be interpreted with caution.

3.5 Active Seeking and Behaviour

Indices from the active seeking task (PropChosen, RT, LT, PD; taken separately) were further compared to parent and observer-rated metrics of language (see Chapter 2.9). No significant associations were observed between scores on EL and RL subscales of the Mullen at all ages and any of the task indices split by Age Point (all *p*s >.1-.8). Additionally, no significant associations were found between the task's indices and vocabulary size on CDI at 14 months (all *p*s >.06-.9), showing no evidence for associations between gaze behaviour in the active seeking task and behavioural phenotype. See Appendix C for individual scatter plots between measures of language seeking and scores on standardised language metrics.

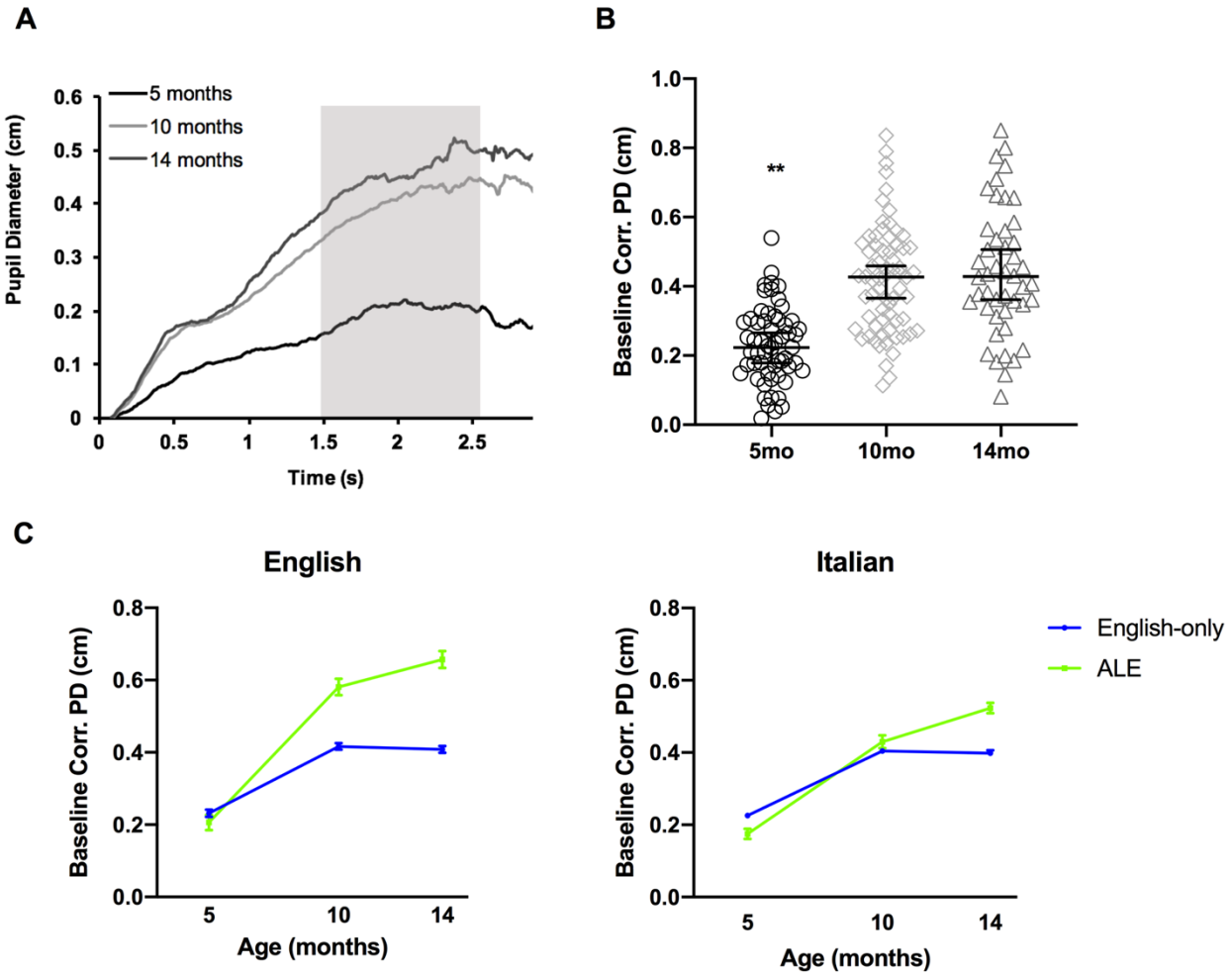

Figure 3.3 Plots demonstrating **(A)** average pupil diameter change over three Age Points, with grey shaded area representing temporal region of interest **(B)** average PD per Age Point, **(C)** pupil diameter for English and Italian stimuli for infants at 5-14 months of age based on model estimated marginal means.

Note. *p<.05, **p<.001. Black bracket denotes group. Error bars depict 95%CI.

3.6 Discussion

The active seeking paradigm used in this experiment revealed some interesting results in the context of research on infant preference for native language and the theory of 'critical periods'. No differences were observed in active seeking of native over non-native language input in any of the Age Points. Although there were developmental changes in reaction time, the finding may reflect the developmental increase in saccade control (Canfield et al., 1995). The finding that reaction time was not dependent on the language of the stimulus further supports this explanation. There were marginal differences in looking time across Age Point and Stimulus, apart from an increase in looking time to English stimuli, which suggested that there may be an overall preference for English, although this was not a consistent metric on an individual level nor was it related to language outcomes. There are, however, age-dependent changes in pupil dilation in response to language stimuli. In addition, there were significant effects of age, language of stimulus and individual language experience which indicated that changes in pupil diameter were not simply driven by maturational factors (Brown, Connelly, Nickols, & Neville, 2015). There were increases in pupil dilation towards English phrases in infants with additional language exposure, which may be related to cognitive effort in language processing. Overall, the patterns observed appears to suggest that there is no clear evidence of native language seeking over the first year of life, which contrasts previous literature in the field of infant communication development. Implications of these findings are considered relative to current understanding of infant speech perception.

3.6.1 Is there evidence for infant 'preference' of native language?

The existing body of literature suggests that infants begin to seek out linguistic input from the environment, and show increasing preference for listening to their native language (Byers-Heinlein & Fennell, 2014; Gervain & Mehler, 2010; Kuhl et al., 2006). The study was set up to explore whether infants were seeking linguistic input through an active choice

paradigm, and investigated how this behaviour was affected by age and language experience of the infant. Gaze data suggested that infants chose English and Italian videos equally, and that reaction time was not affected by the language of the stimulus nor individual language experience. Infant 'preference' towards their native language was not supported by present findings, as overall proportion of saccades made was not above chance level for the native and non-native languages. The findings are in contrast to previous literature (Elsabbagh, Hohenberger, et al., 2013; Gervain & Mehler, 2010; Pons et al., 2009), which showed significant increases in infant 'preference' towards the native speech sounds. The discrepancy could be explained by use of cross-sectional design, as well use of phonemes or vowels by past investigations, rather than active choice and naturalistic speech used in the present study. Task differences are important to note, as differentiation of syllables (i.e. infants looking for longer towards the sound of a native vs. non-native syllable) may not fully reflect preference nor functional specialisation towards native language processing.

Additionally, Elsabbagh, Hohenberger and colleagues (2013) employed a modified familiarization-preference procedure (i.e. auditory habituation paradigm) to native and non-native syllables, while Pons and colleagues (2009) used a passive viewing paradigm and measured looking time. Both studies found differences between 6 and 10-11month olds in their ability to process native relative to non-native sound contrasts. It should be noted that researchers not only used passive viewing methods, but also measured the time for infants to dishabituate or lose interest in the stimuli. Stimuli used in the active seeking task however, were multimodal and highly attractive visually, which could mean that there was a ceiling effect in looking behaviour.

In the present task, using a gaze-contingent paradigm with limited training period allowed the capture of more naturalistic choice responses in infants. Specifically, the present task required an 'active' response from the infants, which could explain inconsistencies with

previous literature. A recent review summarised that while infants were able to discriminate between visually possible and impossible events, toddlers failed to complete search tasks that were hypothesised to engage the same cognitive mechanisms (Keen, 2003). It was suggested that the discrepancy between infant and toddler performance was due to task differences i.e. passively reacting to stimuli in the environment required less cognitive effort than driving a response (which also requires prediction formation and planning). Therefore, 'passive' looking paradigms prevalent in infant speech perception literature (Bosch & Sebastian-Galles, 2001; Elsabbagh, Hohenberger, et al., 2013) may indeed lack environmental validity to adequately capture native language preference. Using a gaze-contingent paradigm in this task allowed to capture active choice behaviour. Additionally, tasks that previously showed preference for 'native' speakers have often used different actors for familiar and unfamiliar language stimuli who are native speakers of the respective languages (Begus et al., 2016; Souza et al., 2013). It is therefore difficult to separate 'preference' for speech/language versus preference for a familiar individual on an experimental level.

The active seeking task revealed notable differences between native and non-native language processing. Infants showed increased looking time and pupil dilation to English videos at 10 months of age. The finding is consistent with literature on increased preference towards the infant's native language in the second half of the first year of life. It has been reported that 10 months is a key period in which the infant experiences 'perceptual narrowing' and demonstrates increased discrimination abilities to sounds present in their native language. Increase in looking time at 10 months further coincides with infant's ability to understand their first meaningful words (i.e. between 10-12 months, (Bates, 2014)). Research by Gervain & Mehler (2010), Werker (1989) and Werker & Tees (2005) suggested that a combination of biological and experiential factors facilitate discrimination of speech sounds and infants showed a sharp increase in preference towards native speech from 8 months of age. Kuhl and

colleagues (2006) found that infants looked consistently longer towards the speaker of their native language, and were also increasingly better at differentiating subtle phonetic contrasts present in their native language from as early as 6 months. Therefore, it could be argued that once infants have made the choice in this task, the processing of the stimulus was affected by both age of the infant and familiarity of linguistic input.

3.6.2 Effects of language experience on language seeking.

Analysis of infants with Additional Language Experience showed slower reaction time to stimuli at 5 months and reduced looking time to English stimuli at 10 months relative to the English-only group. However, no differences were observed between the proportion of English videos chosen, nor were there differences in basic gaze metrics (LT, RT) in processing of non-native Italian stimuli. These findings contrast previous research that found increased discrimination of native and non-native languages in bilingual infants relative to their monolingual peers (Albareda-Castellot et al., 2011; Bosch & Sebastian-Galles, 2001). It should be noted that the ALE sample was reported to receive a greater variety of language experience (rather than quantity of exposure), and may indeed have less exposure to English.

Lack of differences in active seeking of language, looking or reaction time in infants with ALE can also be explained by differences in how discrimination is defined experimentally. For instance, one study with 4-month-old Catalan-Spanish bilinguals showed longer looking time towards the unfamiliar English speech, and interpreted this as evidence towards perceptual narrowing (Bosch & Sebastián-Gallés, 1997). Specifically, this study showed that when infants have to discriminate between one of their native languages and a non-native language, it takes them longer than monolinguals to orient towards their native language.

While no clear differences were observed in the language choices made between English-only and ALE groups, there were differences in total looking time and pupil dilation responses between groups. Taken together, present findings suggested that this delay can be explained by added cognitive load of discrimination between two phonetically similar inputs. Pupil dilation data further supported this argument, due to differences observed based on infants' language experience (infants with ALE showing increased PD at 10 and 14 months), as well as the language of the stimulus itself (higher PD for English, driven by the ALE group).

One of the underlying mechanisms behind changes in pupil size has been recognised as changes in mental effort in areas of basic arithmetic (Borys et al., 2017; Bradshaw, 1968), working memory (Goldinger & Papesh, 2012; Otero et al., 2011) and language processing tasks (Hyönä et al., 1995). Changes in pupil diameter have therefore been used as an index of mental workload in both adult and child populations (Marshall, 2002). In infancy, changes in PD have also been reported in several higher-order processing domains. Hepach and Westermann (2013) found that while there were no looking time differences between 10 and 14 month olds when viewing highly emotional videos, pupil dilation analysis showed increased PD at 14 months in response to incongruent voice and action expressions of emotion (Hepach & Westermann, 2013). These metrics further showed greater sensitivity than looking time measures (Jessen et al., 2016; Sirois & Jackson, 2012) as well as the ability to capture the more subtle developmental changes that occur in infancy and early childhood (Addyman et al., 2014; Hepach & Westermann, 2013).

Several studies within bilingualism research note additional cognitive load during language processing in infants and children (Genesee, 1989; Kovács & Mehler, 2009). Individual language experience is therefore important to consider, as learning two languages simultaneously requires separation of those languages in visual (Sebastián-Gallés et al., 2012;

Weikum et al., 2007) and auditory (Bosch & Sebastian-Galles, 2001) domains. The added complexity may in turn impact the way language is processed in early infancy.

Lastly, a recent report by Byers-Heinlein and colleagues (2017) argued that infants from bilingual environments control the languages they perceive. In a series of language switching tasks (i.e. when a portion of a phrase or an additional phrase is substituted with words from a different language), it was found that bilingual infants showed increased pupil size when processing switched versus same-language sentences. These responses were similar to adult performance, and it was suggested that bilinguals may have an advantage in navigating complex language environments by forming early representations of native vs. non-native and dominant vs. non-dominant distinctions (Byers-Heinlein, Morin-Lessard, & Lew-Williams, 2017). Results from the Active Seeking Task are somewhat supportive of this view, although further investigation of the ALE group would be necessary to assess their discrimination abilities to represent words in separate language systems.

3.6.3 Limitations and conclusions.

It should be noted that neither gaze nor pupil dilation indices were associated with cognitive or behavioural metrics in a group analysis. This contradicts previous findings from infant speech perception tasks. Tsao and colleagues found that phonetic perception at 6 months (measured through HTP) was associated with language ability at 2 years (Tsao et al., 2004) and higher discrimination ability of native (but not non-native) speech sounds predicting better language skills at 12 months (Conboy, Rivera-Gaxiola, et al., 2005). The inconsistency with previous literature could be explained by differences in behavioural metrics, task design or statistical methods, which is common difficulty in evaluating research on early speech perception (Cristia, Seidl et al., 2014). Further exploration of dimensional associations between gaze and behaviour will be featured in Chapter 5, where modelling is used to map out individual

variation in active language seeking, EEG-based measures of language processing and language ability at two years.

Limitations regarding individual language experience are addressed in the general discussion of this chapter (see Chapter 3.15). Nonetheless, initial findings from the present task suggest that larger samples of infants from multilingual backgrounds are warranted to explore early differences in language processing behaviour.

Overall, the active seeking task revealed some important age and language processing differences in typically developing infants. In contrast to the previous literature, there was limited evidence for preference of native vs. non-native linguistic input, which can be attributed to task differences. It can be concluded that looking time and pupil diameter responses (separated by stimulus language and language experience) may be used as potential behavioural correlates of specialisation in further analysis, as they showed highest sensitivity to cognitive effort, while associations with behaviour are limited at this stage.

3.7 Eye Tracking Task 2: Development of Audiovisual Speech Perception

Audiovisual matching task (Task 2) was designed to capture another aspect of behavioural expertise, namely the narrowing of intersensory speech perception between 5 and 14 months of age. In the previous task, participants showed differences in the processing of infant-directed native and non-native speech based on their age and language experience, while the present experiment looked at how infants gain expertise in processing speech information within their native language, both within the auditory and visual domains.

Literature on the emergence of speech perception has argued that infants not only display preference towards their native language (Moon et al., 1993), but also become tuned to its phonological characteristics over the first year of life (Altvater-Mackensen & Grossmann, 2015). Visual input (i.e. mouth movements) is important to consider in addition to sound information as a more naturalistic representation of early social interaction and language learning (Burnham et al., 2013). Infants appear to be sensitive to congruent speech and face information from a young age, preferring to look at congruent vs. incongruent audiovisual articulations (Grieser & Kuhl, 1988; Kuhl & Meltzoff, 1982; Mercure et al., 2019; Patterson & Werker, 1999). Due to apparent robustness of this phenomenon, infant ability to match audiovisual speech information was explored in the following task as a candidate behavioural marker of specialisation.

While some researchers have suggested that matching of auditory stimuli and incoming visual information is innate and present throughout early development (Kuhl & Meltzoff, 1982; Shaw, Baart et al., 2015), others argued that the skill develops in parallel to perceptual attunement and increasing discrimination ability towards the native language within the first year of life (Lewkowicz & Hansen-Tift, 2012; Pons et al., 2009; Saffran et al., 2007). Pons and colleagues showed that Spanish infants were performing audiovisual matching (higher looking time towards visual stimuli that corresponds to the auditory information, also termed

Multisensory Redundancy) of Spanish 'va/ba' sound in 6-month-olds, but not 11-month-olds or Spanish adults. On the other hand, English infants and adults demonstrated audiovisual matching the sounds and visible speech consistently, which suggested that experience with a sound contrast is necessary to maintain sensitivity in non-native language categories.

It should be noted that combined audio and visual information enhances discrimination, perception and encoding of linguistic information due to increase in salience (Calvert, Spence et al., 2004; Lewkowicz & Ghazanfar, 2009). It was further suggested that intersensory matching underpins production of infants' first speech sounds (Kuhl, 2000) and predicts later vocabulary size (Altvater-Mackensen & Grossmann, 2015). Several experiential factors can preclude narrowing in audiovisual speech integration i.e. multilingual households, cochlear implants due to hearing loss or presence of a Deaf parent or caregiver (Astheimer et al., 2016; Mercure et al., 2019; Peterson et al., 2010). However, generalisation of previous studies in the field are somewhat limited by their use of cross-sectional design, where longitudinal/prospective methods would allow to see dimensional chance in these abilities with increase in language experience.

Another important aspect of speech perception, is association of mouth shape and sound. It has been found that infants pay attention to the mouth of the speaker (Barenholtz et al., 2016), and this mechanism is particularly important during key phases of language acquisition (Król, 2018; Lewkowicz & Hansen-Tift, 2012; Werker & Yeung, 2005; see Task 3). The ability was elevated in infants who were mimicking the shape of the sound with their own mouths (Yeung & Werker, 2013). Associations between shape and sound have been observed in children and adults when exposed to nonsense words (Maurer, Pathman, & Mondloch, 2006), which suggested that audiovisual matching facilitates language learning. Infants from 4 months of age were also found to look longer at incongruent sound and shape pairings, although they required both more sound information relative to adult participants

(Ozturk et al., 2013). One of the principle limitations of existent research is that the paradigms are largely based associations between exaggerated and/or still images of mouth shapes and artificially generated sounds rather than mouth gestures present during naturalistic speech. Even though the rigorously controlled experimental stimuli increases interval validity of the design and allows more direct comparisons between infant and adult performance, there is still little understanding of emergence of spontaneous audiovisual matching during speech perception, as well as the effects of individual differences on this ability.

3.7.1 Present study.

The task is an adaptation of the classic audiovisual matching paradigms and aims to replicate age-dependent effects on intersensory matching as well as predicting sound information from static mouth shapes. Note that previous literature described above assessed syllable production only, and audiovisual matching of whole sentences has not been observed until 12 months of age (Lewkowicz et al., 2015). It was predicted that infants would be able to correctly match audio and visual speech information above chance level from 5 months of age. It was further expected that infants would show an increase audiovisual matching (higher proportion of LT to matched vs. mismatched audio and visual speech information) between 5 and 10 months. In addition, audiovisual matching was expected to decrease by 14 months due to reduced engagement with the task. For the subgroup of infants with additional language experience (ALE), it was predicted that audiovisual matching would not be present until 10 months of age and would be present at 14 months as infants continue to focus on redundant speech information for longer than the English-only peers.

An additional aspect of the study looked at infant's ability to predict syllable production from a still image of the mouth shape. This is a much more complex ability, and it is expected that infants will not be able to correctly predict the correct syllable from the mouth shape until 14 months of age. It was further expected that higher individual predict/matching scores would

be related to higher levels of language ability measured through a behavioural assessment (Mullen, 1995) and parent report measure of language comprehension (Fenson et al., 2007).

3.8 Methods

3.8.1 Participants.

Participants for this task were the same as described in Task 1 (Chapter 3.2.1).

3.8.2 Stimuli and Design.

Visual stimuli for the discrimination task consisted of two videos (side by side). Each video featured a native English female speaker articulating a repeated syllable soundtrack (i.e. "ba ba ba"). The videos presented on every trial were contrasting syllable soundtracks (i.e. /ba/, /da/, /ma/ and /ga/). The presentation of the syllables was counterbalanced so that in a single trial the contrast would either be /ba/ and /ga/ or /da/ and /ma/, counterbalanced for order of presentation and side of the screen for each participant. The task block began with presentation of static videos (Predict Condition), followed by a central fixation cross, and then two animated videos (Figure 3.4). The video stimulus entailed 5 consecutive repetitions of the syllable, with an interval of approximately 0.5 second between repetitions and a 1 second inter trial interval. Each utterance started and ended with the mouth completely closed and in a neutral position. For the initial video stills (Predict Condition), the screen shot was chosen as the initial mouth position before the utterance began, in order to maximise the visibility of vowel shape (Figure 3.4). In the following Match condition, the video with the full mouth utterance was played. The eye gaze was always directed toward the infant. All videos were centred around the face of the speaker against a dark grey background (RGB 222 222 222). The two video frames (20cm x15cm for each video) were positioned on the right and left side of the screen with a 3cm gap from the edge and against a black background (RGB 0,0,0) to maximise attention. Visual angle was approximately 112.6 degrees (112° 37' 0.19").

Auditory stimuli for the discrimination task consisted of recordings of /ba/, /da/, /ma/ or /ga/, spoken by the same speaker as featured in the videos. The stimuli were recorded in a quiet room at sampling rate of 50 frames per second and presented at 25 frames per second. The same auditory stimulus was played for the Predict and Match condition within each task block. This ensured better pairing between auditory and visual parts of the task. One block of 8 trials was presented in Part 1, and two blocks of 8 trials each were presented in Part 2 of the task.

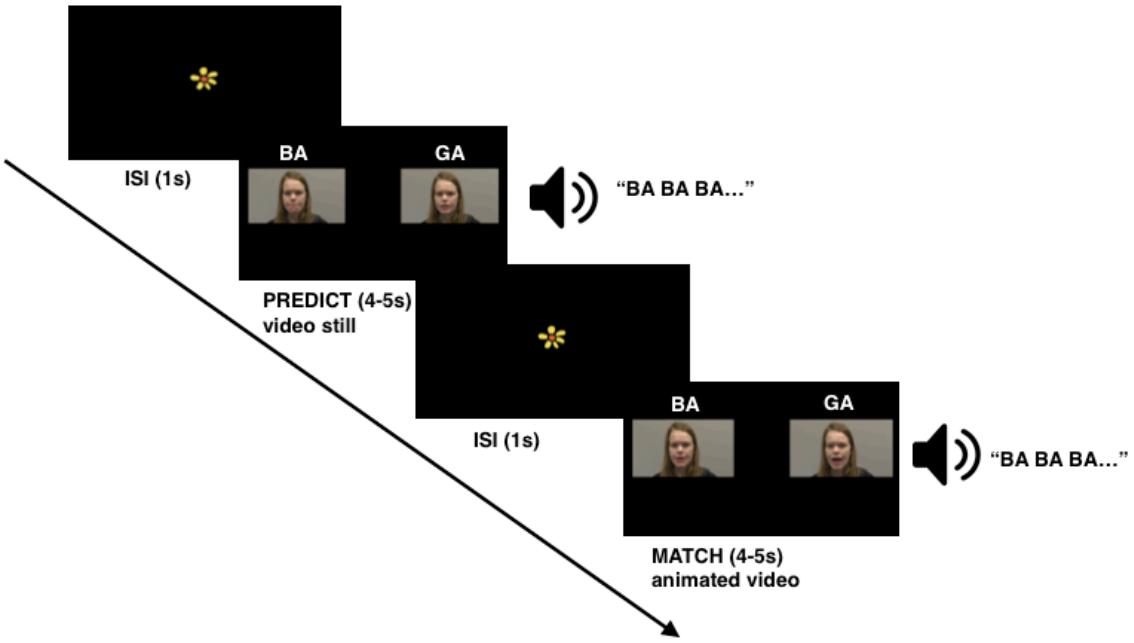

Figure 3.4 Schematic representation of the order of stimuli in the audiovisual matching task. Note that stimuli parts were matched for /ba ba ba/ vs. /ga ga ga/ and /da da da/ vs. /ma ma ma/ (counterbalanced for location on the screen). Adapted from Figure 1 in Pons and colleagues (2009).

3.8.3 Procedure.

As described in Task 2, infants were seated on their parent's lap in a quiet experimental room in front of the same eye tracker (for details on the size and acquisition rate see sections 3.2.2 Stimuli and apparatus and 3.2.3 Procedure). Proportional Looking Time to each side was measured as the main dependent variable for Predict and Match conditions (calculated as Prop

LT = Match LT / Match LT + Non-Match LT). AOIs for this task were defined as the entire video (right vs. left), for which a match was defined as proportion of look at the side which corresponds to the audio stimulus. There were no trials where both videos were mismatching, and eye-to-mouth looking ratio was not investigated in this task due to the small size of the stimulus videos.

3.8.4 Data cleaning and analysis.

Data was pre-processed in MatLab®(R2017a) and analysed in SPSS (IBM, V23). Firstly, data was considered valid if the eye tracker detected at least one eye, and if the participant was looking at one of the AOIs (rather than any other point on the screen). Mean Prop LT (looking time from valid samples from first frame after the fixation point offset) was calculated for each participant separately for each video. The proportion of data lost, per trial, had to be equal to or less than 50% of the total looking time to be included. Notably, the data quality criteria were lower than in Task 1, due to poorer data quality on this task. Additionally, each participant had to contribute at least 5 ‘good’ trials in order to be included in the final analysis. As can be seen from Table 3.3, the amount of data retained from the task was relatively high using these conservative cleaning tools. There were no significant differences in data retention across participant visits, the task was equally engaging. Data cut off of 50% proportional looking time has decreased attrition rate while remaining conservative in regards to data quality, whereby the task is therefore considered sufficient to obtain the infants’ attention and return an adequate amount of trials.

Table 3.5 *Sample size and trial numbers retained following gaze analysis of audiovisual matching task following data cleaning steps. Predict and Match columns denote mean and standard deviation of trial numbers for the respective conditions.*

Age Point (N visits)	*Original sample*			*Prop Valid (≥50%)*			*Trial Total (≥5)*			*Overall Retention Rate*
	n	*Predict*	*Match*	*n*	*Predict*	*Match*	*n*	*Predict*	*Match*	*N%*
5m (45)	43	14.8 [1.21]	15.8 [1.21]	41	12.71 [3.14]	13.71 [3.45]	41	12.71 [3.14]	14.21 [2.71]	95.3%
10m (48)	46	13.9 [2.72]	14.9 [2.72]	44	12.45 [3.64]	13.77 [3.54]	43	12.72 [3.22]	14.23 [2.9]	93.5%
14m (39)	28	13.7 [2.99]	14.7 [2.99]	28	12.78 [3.37]	13.64 [3.69]	27	13.22 [2.5]	14.07 [2.96]	96.4%

Note. Numbers between N visits and original sample differ as not all infants who attended their visit provided ET data (due to tiredness or issues with calibration or equipment).

Based on the online coding of the experiments (with pre-defined AOIs as the whole frame around the video), Prop LT was calculated towards matching and mismatching AOIs for both Predict and Match trials for each individual infant. To identify if infants were able to correctly match audiovisual information, a proportional score was calculated for looking time towards matching vs. non-matching audiovisual information during Predict and Match trials in the task. This was done by dividing the looking time at the matching side of the screen by the sum of total looking time towards the matching and mismatching audiovisual information (Prop LT Match/Predict Trials = Match LT / Match LT + Non-Match LT; Pons et al., 2009). Higher proportional value would suggest higher looking time towards the matching vs.

mismatching AOI. For statistical analysis of this data, Linear Mixed Models were run for Match and Predict conditions, with Age Point as a fixed factor and Trial Number and Sex included as covariates. As described in the analysis for Task 1 above, all models were initially run with the total sample, followed by an additional model with Language Experience added as a factor (English-only vs. ALE). Lastly, the analysis looked at the dimensional relationship between Prop LT to the Matching audiovisual stimulus and language ability, measured through scores on the Expressive and Receptive Language subscales on the Mullen (1995) at each Age Point as well as the total number of words Understood and Understood and Said on the CDI (Fenson et al., 2007) reported by the parents at the 14-month visit. Note that for some of the results outlined below, effect sizes for non-significant *p* values are not reported as the partial eta squared statistic was lower than 0.0001 and confidence intervals crossed the zero value.

3.9 Results

3.9.1 Infant matching of audiovisual speech information.

Firstly, Prop LT to Matched audiovisual stimuli were compared between Part 1 and Part 2. There were no significant differences revealed (all *p*s>.15), and all trials are collapsed across Part for further analysis. Then, Prop LT was entered into a t-test split by Age Point, which revealed that proportional looking time to the matched vs. mismatched stimulus was not significantly different than chance level (50%) at 5 (*p*=.106), 10 (*p*=.228) or 14 (*p*=.222) months. Additionally, Prop LT was compared between right or left side of stimulus presentation averaged over condition and did not find significant side bias for any of the three Age Points (all *p*s>.53).

Audiovisual matching was submitted to a series of LMMs, to look at effects of Age Point and Language Experience. In the Match condition, there was no effect of Age Point (*p*=.68). Due to lack of Age Point effects, it can be suggested that performance on the

audiovisual matching task did not change with age. The effect of covariates Trial number (*Wald Z*=1.01, *p*=.31) or Sex as a covariate (*Wald Z*=-.110, *p*=.912) were not significant predictors in the model. Adding Language Experience to the model did not improve fit and the model did not reveal any main effects of Age Point (*p*=.59) or Language Experience (*p*=.373). The covariate parameters were non-significant predictors in the model TrialNo (*Wald Z*=.934, *p*=.35) or Sex (*Wald Z*=-.16, *p*=.873).

For the Predict condition, the model did not reveal a main effect of Age Point (p=.919). Covariates of TrialNo (*Wald Z*=.326, *p*=.744) or Sex (*Wald Z*=-.038, *p*=.97) were also not significant. Addition of Language Experience did not return a significant effect of Age Point (*p*=.92) or Language Experience (*p*=.942), suggesting that there were no significant differences in Prop LT to matching stimulus for audiovisual matching of still images. No significant effects of covariate parameters TrialNo (*Wald Z*=.992, *p*=.321) or Sex (*Wald Z*=.238, *p*=.812).

3.9.2 Changes in looking to stimulus over time.

Next, a regression analysis was carried out to look at changes in looking time over time to reveal further information about infant engagement with the task. Trial numbers were recalculated from 1-16 to 1-8 depending on the position of the trial from the start of the block. For this analysis, Age Point and Condition were added on first step, followed by Trial Number. Linear regression showed a non-significant effect of Age Point (*b*=-.001, *t*=.-.633, *p*=.527, *CI*[-.005 .003]) nor Condition (*b*=.008, *t*=.545, *p*=.58, *CI*[-.020 .035]) on Prop LT to matching audiovisual stimulus side. The model was also not significant at this step (*p*=.706). Addition of trial number using significantly improved model fit (*r* change=.003, X^2=4.72, *p*=.03), although overall model did not reach significance (*p*=.114). Trial number was a significant predictor in the model (*b*=-.007, *t*=-2.17, *p*<.030, *CI*[-.013 -.001]), suggesting an overall reduction in proportional looking time over trials in a block (which is expected as infants lose interest in the matching stimulus and begin showing novelty preference; Figure 3.5). Based on

the figure, it appears there is a reduction in looking time in 10 and 14 month groups, but an increase at 5 months; although this did not reach significance. There were no correlations between predictors as tolerance and average variance inflation factor (VIF) were around 1, confirming that multicollinearity was not a problem in this dataset. Another model was run with Language Experience as an additional factor, which did not improve model fit (*r* change= .0, X^2=.709, *p*=.4) and it was not a significant predictor in the model (*b*=-.013, *t*=-.842, *p*=.4, *CI*[-.044 .018]) and therefore excluded. Again, there were no correlations between two model predictors and both tolerance (.999) and VIF statistic (1.05) suggested that there was no concern of multicollinearity. It should be noted that trial counts refer to presentation of trials within each task block, with a total of 3 task blocks repeated during each eye tracking session.

As no significant differences in audiovisual matching were observed, the models were repeated with data from only the first two trials for both Predict and Match conditions (when LT and therefore attention was highest towards the task stimuli). However, there were no significant differences in performance on the task in this model, and there were no effects of Age Point ($F(273)$=.617, *p*=.54, η_p^2=.0012), Condition ($F(235)$=.475, *p*=.49, η_p^2=.001), nor Language Experience ($F(215)$=.499, *p*=.50, η_p^2=.001) observed on Prop LT over the first two trials.

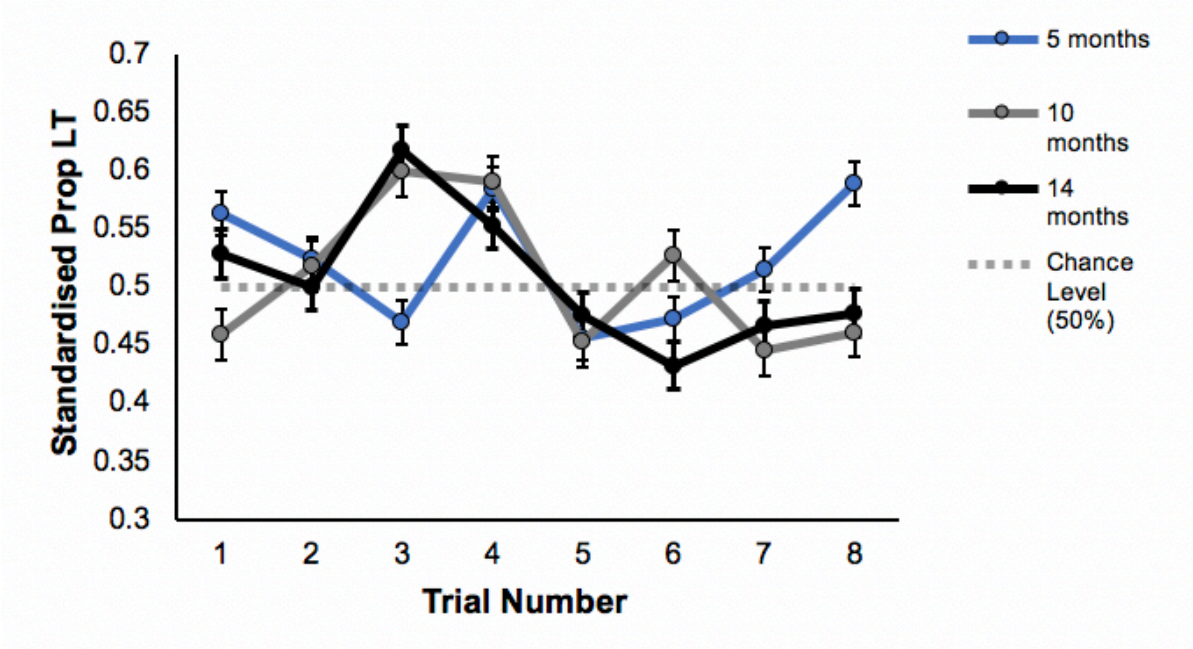

Figure 3.5 Changes in Proportional Looking Time across trials in audiovisual matching task block. No differences across Age Point in reduction of LT towards matching target. *Note*. Error bars represent 95% CI.

3.9.3 Individual stability of audiovisual matching.

Next, stability of individual audiovisual matching responses were examined over time. There were no significant correlations between Prop LT at 5 and 10 or 10 and 14 months of age (*r*s -.019-.067; *p*s .58-.9). This was maintained when controlled for Condition (*r*s -.177- -.60; *p*s .28-.72). These findings suggest no internal consistency of performance on audiovisual matching on an individual level.

3.9.4 Behavioural comparisons.

Lastly, Prop LT to matching audiovisual information was subjected to a dimensional analysis with behavioural data, irrespective of Age Point or Language Experience. For the Match condition, there was no significant association between Prop LT and scores on the EL and RL subscales on the Mullen (*p*s .15-.69) nor number of words Understood nor Understood and Said on the CDI (*p*s .42-.21). For the Predict condition, there were no associations between

Prop LT and scores on the Mullen subscales (*p*s .15-.69) nor number of words Understood nor Understood and Said on the CDI (*p*s .42-.21), which was not unexpected due to lack of significant effects of age or language experience reported in the main analysis.

3.10 Discussion

The ability to perceive auditory and visual information during speech as a unified event is a n integral component of the ability to understand and produce language (Pons et al., 2009). The task described in this section aimed to reproduce previous findings on infant intersensory matching of speech information, which has been reported consistently from 4.5-5 months of age (Kuhl & Meltzoff, 1982; Mercure et al., 2019; Patterson & Werker, 1999). However, neither age nor language experience effects were observed on audiovisual matching. Similar to the results reported in Task 1, matching ability was not specific to the native language of the infant nor their individual level of language experience. Contrary to previous literature, infants were not able to Match the visual and auditory information nor Predict auditory presentation of a syllable to a corresponding still image of a mouth shape. The findings suggest that the ability may not be a spontaneous response in pre-verbal infants. Additional exploratory analyses revealed no significant preferences in the first two trials of the task. Looking time to matching vs. non-matching intersensory stimuli was not associated with early metrics of language ability, which is not a surprising result due to looking time not differing from chance level across participant ages. Overall, there are some considerable reservations around the reliability of looking time to native syllables as an index of perceptual narrowing in early infancy or a predictor of EEG-based markers of specialisation, which are considered below.

Results from this task do not appear to support integration of auditory and visual speech perception in the first year of life, as infants between 5 and 14 months of age were looking at congruent information at chance level (51-52%). Note that this is considerably lower than 73% matching reported by Kuhl & Meltzoff (1982) and 65% reported by Patterson &Werker (1999).

Patterson and Werker suggested that the reduction in matching in their study was likely due to use of using more complex face information (including hair, ears, neck and shoulders) relative to the female face with obscured features used in the original 1982 interpretation of the task. A more recent unpublished replication of this task design further reported that 4 and 11-month-old infants look at matching audiovisual sentences at chance level when a naturalistic face is presented (Kervran, 2015). Differences in task stimuli between current task and the design typically used in the field could further explain lower matching scores observed in the present study. Specifically, stimulus design included the full face and upper body of a female speaker as well as two smaller videos side-by-side, which further increased task demands.

3.10.1 Do infants spontaneously engage in audiovisual matching?

No evidence to support audiovisual matching in either the Match nor Predict conditions was observed in the present task. This finding was contrary to previous investigations that showed elevated looking time to audiovisual matches as well as age effects of age on audiovisual speech perception (Altvater-Mackensen & Grossmann, 2015; Danielson et al., 2017; Pons et al., 2009). Further, Mercure and colleagues (2019) reported reduced sensitivity to audiovisual congruency in bimodal bilinguals (i.e. hearing infants with Deaf mothers), which suggested that speech and language experience is essential for development of this ability. There are several methodological differences which may explain differences between results of the Audiovisual matching task described above and previous literature. One of the possible explanations is that audiovisual matching tasks often use vowel sounds only (Altvater-Mackensen & Grossmann, 2015; Danielson et al., 2017). It should be noted that intersensory matching of syllables rather than vowels is complex and findings to support development of this ability have not been widely explored in the literature (Pons et al., 2009). It has been reported that vowel processing occurs earlier in development (Kuhl et al., 1992; Trehub, 1973; Werker & Polka, 1993), and that development of consonant perception is affected by individual

levels of experience (Bertoncini & Mehler, 1981; Best et al., 2001; Moffitt, 1971). The adapted version of the task included in this chapter aimed to test whether this ability is present in young infants across similar age ranges, however due to complex task demands/ decreased interest in stimuli this response was not observed.

Pons and colleagues (2009) reported perceptual narrowing towards the native sound contrast between 6 and 11 months of age. Specifically, Spanish but not English-speaking infants lost their discrimination abilities of the /va/-/ba/ contrast (a non-native language category in the Spanish language), which is in line with the idea of experience-dependent specialisation. The task described above differs to the paradigm used by Pons on several levels. Firstly, the study by Pons and colleagues featured practice/familiarisation trials where auditory information was repeated several times interspersed among the test trials. Familiarisation with the auditory information only may have increased infants' attention to this contrast, and in turn enhance their audiovisual matching performance. The task designed in the present work, however, did not include 'test' trials, and, in fact, familiarisation with the stimuli across trials showed a decrease in proportional looking time over the 8 trials presented. Secondly, individual familiarity of phonetic contrasts was not controlled for, focusing on phonemes which reflect the first infant babbles due to the large variability of different languages of infants in the present study. Although infants may begin to combine vowels and consonants in spontaneous vocalisations such as 'ba-ba', 'ma-ma' and 'da-da' around 3-4 months of age, present findings suggest that there is limited evidence for spontaneous integration of speech information from another speaker. Indeed, a series of three experiments with 4-5 month olds showed evidence that was both consistent and inconsistent with audiovisual integration (Desjardins & Werker, 2004). Researchers suggested that infants may not consistently use audiovisual matching during processing of speech information, as paying attention to either the auditory or visual component of the stimulus was sufficient in evoking discrimination/habituation abilities.

3.10.2 Engagement with task stimuli over time.

The infants looked longer towards the matching stimulus side at the start of the experiment. This was followed by a decrease in proportional looking time to matching audiovisual information across all age points. The nature of observed behaviour is unclear, yet it can be suggested that complexity or small size of the stimuli could have reduced attentional engagement. One important limitation of infant eye tracking studies is the common practice to exclude infants from the main analysis if they do not reach a specific looking time threshold (Johnson & Zamuner, 2010). Due to the moderate sample size within these tasks, as well as the focus on age-dependent change in performance, no participants were excluded based on 'poor' audiovisual matching ability. Following this strategy would exclude infants who are not able to perform audiovisual matching. As well as reducing sample size, employing the strategy would risk overlooking individual variation in early speech processing abilities. It could also be argued that some aspects of the task (i.e. the Predict condition) were too cognitively complex for the infants, as pre-verbal infants may not be readily detecting syllabic information from the mouth shape alone. Further investigation of this task warrants observation of corresponding infant mouth movements when viewing matching or mismatching audiovisual stimuli as well as presence of selective attention to the mouth during presentation of audiovisual stimuli (Lewkowicz & Hansen-Tift, 2012; Patterson & Werker, 1999).

Findings of this experiment did not reveal associations between looking time towards matching audiovisual information and behavioural measures of language abilities. This is in contrast to the study by Alvater-Mackensen & Grossman (2014), who reported that integration of auditory and visual speech in 6-month-olds was related to vocabulary size at 12 months. There was also evidence to show that children with diagnosis of ASD, who experience an increased incidence of language and communication difficulties, showed poor audiovisual speech integration (Guiraud et al., 2012; Smith & Bennetto, 2007; Taylor, Isaac, & Milne,

2010). Interestingly, MacKain and colleagues (1983) carried out a study with 5-6 months old infants and found, even with adequate counterbalancing measures in place, preference to matching versus mismatching audiovisual displays only emerged when considering the right side of the display. The authors reasoned that this may reflect left hemisphere specialisation in language perception in infancy, however exploratory analyses of side bias did not support the hypothesis in the present experiment. Absence of association was not unexpected relative to proportional looking time not being higher than chance level for all ages. Generalisation of these findings is limited due to a relatively small sample size and high variability in language ability reported within the infant sample.

In conclusion, the audiovisual matching task did not provide evidence of audiovisual matching in pre-verbal infants, and absence of expected effects of age and language experience raise important questions about current experimental practices as well as the actual developmental timing of this ability. Specifically, audiovisual matching may be affected by size of the stimulus, type of auditory information as well as complexity of the visual stimulus, which need to be taken into account when interpreting existent literature. Previously reported associations between audiovisual matching and early language ability further highlight the importance of task design and language ability metrics. Overall, proportional looking time was not a strong predictor of age or experience-dependent expertise in the first year of life, and is therefore unlikely to be a robust predictor of EEG or phenotypic indices of specialisation.

3.11 Task 3: Selective Attention to Eyes and Mouth for Native and Non-native Speech

The final task included in this chapter was designed to further expand on findings from Task 2 – by looking at progressive shifts in infant selective attention between the eyes and mouth of a speaker throughout the first years of life. Examining age-dependent changes in

attention to different facial features during speech perception is essential to understanding mechanisms behind imitation and subsequent language production (Lewkowicz & Hansen-Tift, 2012; Patterson & Werker, 1999). Individual differences in selective attention based on Age and Language Experience would provide evidence for experience-driven specialisation towards native language in early infancy.

The vast majority of the literature on infant speech focuses on speech comprehension and processing of language. While this has shown age-related changes in several investigations (Elsabbagh et al., 2013; Kuhl et al., 2006; Maurer & Werker, 2014), findings from Task 1 and 2 questioned the reliability of these findings across different task designs. Next, I focused on information sampling during naturalistic speech, a feature of speech processing which might be more sensitive to age-related change. Selective attention to facial features has been reported to change with age, and appears to co-occur with infant mouthing and imitation of vowels occurs from 20 weeks, in preparation for sound production (De Boysson-Bardies, Halle, Sagart, & Durand, 1989; Kuhl & Meltzoff, 1996; Patterson & Werker, 1999). A seminal cross-sectional study by Lewkowicz and Hansen-Tift (2012) revealed age-dependent changes in attention to the speaker's eyes and mouth. Specifically, it was reported that 4-month-olds looked longer at the eyes than mouth, followed by a shift from the eyes to the mouth around 8-12 months. This initial shift around 6 months of age was attributed to infant's first production of babble sounds, where increased attention to the mouth of the speaker used as a source of highly salient information about both native and non-native speech forms during a key stage in language acquisition. The observation of analogous attentional shifts for native and non-native speech suggests that infants did not show preference for English at 8 months, which is in line with the findings from Task 1. By 12 months, it was found that infants shifted their attention back to the eyes, but only for their native language. These observations have been supported by Tomalski and colleagues (2013), who showed that age-related changes in looking to the

mouth between 6-8 months coincide with the onset of canonical babbling. Additionally, researchers found that younger infants look more at the mouth vs. eyes in older infants in observation of naturalistic scenes and suggested that eye-to-mouth attentional shifts are present in real-life processing of communicative information (Frank et al., 2011). Changes in eye-to-mouth looking have also been associated with age-related changes in brain responses to speech sounds (Kushnerenko et al., 2013). It should also be noted that language familiarity was found to be an important modulating factor in speech perception, specifically in that monolingual infants and adults showed higher looks to the mouth than the eyes during perception of an unfamiliar language (Barenholtz et al., 2016; Boisferon et al., 2017). Differences in eye-to-mouth attention has been put forward as an index of second language proficiency beyond infancy.

There are some important differences observed in selective attention in infants from multilingual backgrounds. Firstly, it was found that bilingual infants looked longer at the mouth than the eyes of a speaker by 4 months of age and showed a stronger preference for the mouth at 8-12 months for both native and non-native language stimuli (Pons et al., 2015). Researchers suggested that bilingual infants may rely on redundant audiovisual information earlier and for longer as they acquire knowledge of linguistic structures simultaneously for two languages. Bilingual infants were also shown to pay more attention to the mouth region during perception of emotional information from a face (Ayneto & Sebastian-Galles, 2017), as well as better language discrimination ability at 8 months in a task where only visual information was available (Bosch & Sebastian-Galles, 2001; Sebastián-Gallés et al., 2012). It could therefore be suggested that increased language processing abilities observed in bilinguals (Kovács & Mehler, 2009; Kroll & Bialystok, 2013) are driven by increased mouth looking, a strategy to increase processing of incoming speech information. Notably, Mercure and colleagues (2019) found comparable increases in their looks towards the mouth between 4 and 8 months of age

in monolingual and bilingual infants, albeit bilingual infants showed a bigger increase in looking time to the overall face. In the same study, bimodal bilinguals (hearing infants with Deaf mothers), who experience a reduction in audiovisual speech input, did not show the first attentional shift between the eyes and the mouth between 4 and 8 months of age (Mercure et al., 2019), which highlighted the importance of experience with speech in driving this ability.

One of the main limitations of studies outlined above is that they employ cross-sectional designs (i.e. infants tested once and grouped by chronological age), which limits the interpretation of the dynamic nature of attentional shifts on an individual level. Studies of longitudinal emergence of this ability are therefore warranted. Further, there are a lack of consistent measures of looking behaviour (i.e. Eye-to-Mouth ratio, Proportion of Fixation Duration, Mean/Median Looking Time to AOI); as well as use of different speakers in representation of 'native' and 'non-native' languages, which is likely to generate methodological problems due to preference for a familiar vs. non-familiar faces. These limitations were taken into consideration during design and analysis phases of the experiment below.

3.11.1 Present study.

The present task uses longitudinal design to explore age-related changes in selective attention to facial features for infant directed speech. It was predicted that 5-month-olds in the sample will show a higher Eye-to-Mouth[13] ratio as well as longer Peak and Mean looks to the Eyes than the Mouth than at 10 and 14 months of age. An attentional shift towards the mouth

[13] Eye and Mouth are capitalised as they represent areas of interest which include the respective facial features as well as the surrounding areas.

was expected at 10 months, irrespective of individual language experience. Further, it was expected that by 14 months, infants from English-only households would show a second attentional shift back to the Eyes (increased Eye-to-Mouth ratio) for native nursery rhymes, while infants with ALE were expected to show higher LT to the Mouth for both native and non-native stimuli. This analysis further considered associations between attentional shifts to Eyes vs. Mouth and behaviour. Based on recent findings (Boisferon et al., 2017; Tsang et al., 2018) it was predicted that differences in Eye-to-Mouth looking would be significantly associated with experimenter and parent report metrics of early language skills.

3.12 Methods

3.12.1 Participants.

Participants for this task were the same as described in Task 1 (Chapter 3.2.1).

3.12.2 Stimuli and Design.

The videos were recorded and presented at 50 frames per second against a light grey background (RGB 222 222 222). An animated visual and auditory fixation point was presented between each video, with 3 nursery rhyme videos presented at Part 1 and 4 nursery rhyme videos presented at Part 2 of the task battery. Looking time to Eye and Mouth regions (Figure 3.6) was recorded as the main dependent variable, looking at the effects of age and stimulus language.

The task stimuli consisted of a video presented on the full screen of the Tobii Eye-tracker of a Dutch-English bilingual speaker singing famous nursery rhymes in either English or Dutch (including "Baba Black Sheep", "If You're Happy" and "It's Raining", Figure 3.6).

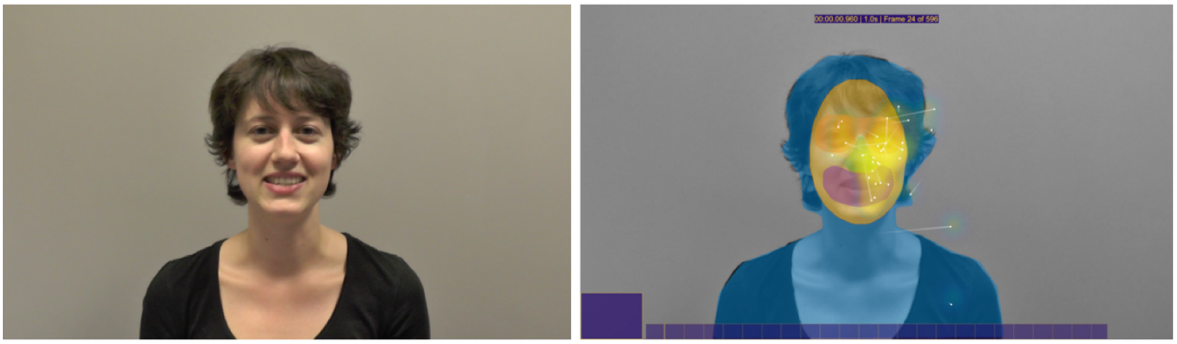

Figure 3.6 Screengrab of an actor singing popular nursery rhyme (left) and visualisation of AOIs (Eyes, Nose, Mouth, Face, Outer face and Body) defined in this task and individual 'hit' points and heat map visualising infant looks, visualised through in-house MatLab scripts (right).

3.12.3 Procedure.

The task was also administered in the larger eye tracking battery, where infants were seated on their parent's lap in a quiet experimental room in front of the same eye tracker (for details on the size and acquisition rate see Chapter sections 3.2.2 Stimuli and apparatus and 3.2.3 Procedure). During each trial in the task, the infants were shown videos of popular nursery rhymes sung in either English or Dutch that were presented on the full screen for 4-7 seconds. Gaze data was acquired for the length of the video and segmented based on AOI offline (see section below).

3.12.4 Data cleaning and analysis.

Data was pre-processed in MatLab® (R2017a) and analysed in SPSS (IBM, Version 23). Overall, gaze data was considered valid if the eye tracker detected at least one eye on the screen. Areas of interest in this task were defined offline using Apple Motion software (Version 5.3.1.) as the areas around the Mouth, Eyes, Nose, Outer Face, Face (which included sum of Mouth, Eyes and Nose) and Body for each stimulus video (see Figure 3.6). Remaining areas

of the screen, i.e. background, were not recorded or analysed further. The videos were then rendered into an MP4 format and exported into MatLab, where Binary Masks (black and white outlines) were created. Eye gaze 'hits' were then scored using in-house scripts (Dr Luke Mason) per millisecond that they entered each pre-defined AOI. Individual trials were included in final analysis if proportion of data lost was less than 50% total looking time, before computing an individual average per nursery rhyme per participant. Due to the small number of trials, infants who contributed data to at least one trial/nursery rhyme were included in the final analysis. Proportional Looking Time (Prop LT) to AOI as well as Peak Looks to each AOI were then exported to SPSS for statistical analysis. Prop LT is defined as 'valid' looking time to AOI per trial, excluding fixation point at the start of the trial. Peak Look is calculated as the longest number of samples in each AOI with a gaze hit (1=gaze true, 0=gaze false) with missing samples of up to and including 100ms interpolated to account for eye blinks and areas of poor calibration. The data was then exported into SPSS for further analysis.

For this analysis, Eye-to-Mouth (ETM) ratio was calculated as Looking Time to Eyes minus Looking Time to Mouth divided by Looking Time to Eyes plus Looking Time to Mouth, where positive values would indicate higher LT to Eyes and negative values would indicate higher LT to Mouth (values between -1 and 1). These calculations are commonly used in to assess infant selective attention during speech processing tasks (Lewkowicz & Hansen-Tift, 2012; Mercure et al., 2019). Two variables will be considered, including ETM ratio and Peak ETM, in order to examine different aspects of looking behaviour. Pre-selecting dependent variables will reduce the overall number of models needed. The dependent variables will be entered into a series of Linear Mixed Models on a single trial level and compared across Age Point, Language of Stimulus, as well as Language Experience, with Sex and Trial Number added as covariates to the model. The alpha level at 0.05 and confidence intervals (CI) reported as estimates of effect size. Post hoc tests for significant interaction terms in Linear Mixed

Models (LMMs) were carried out using pairwise comparisons of estimated marginal means using Sidak adjustment to account for the multiple comparisons problem (West, 2009). Note that visualisation of this data will also include averages for Peak looks per Age Point or Language Experience group and some exploratory analysis of looks to face/outer body.

Table 3.6 *Sample size and trial numbers retained following cleaning of the Nursery Rhymes task. The columns provide information about the mean number of trials as well as the standard deviation.*

Age Point (N visits)	*Original sample*		*Prop Valid (≥50%)*		*Overall Retention Rate*
	n		*n*		*N%*
5m (45)	43	6.21 [1.56]	37	6.08 [1.65]	86%
10m (48)	47	6.00 [1.81]	43	6.04 [1.70]	91.5%
14m (39)	31	6.00 [1.73]	26	6.26 [1.53]	83.8%

Note. Numbers between N visits and original sample differ as not all infants who attended their visit provided ET data (due to tiredness or issues with calibration or equipment).

3.13 Results

In order to assess overall engagement with the social stimulus, Prop LT to the Face (which includes Eyes, Nose, Mouth and Outer-face regions[14]) were compared in a univariate ANOVA with Age Point (5, 10 and 14 months) and Language (English vs. Dutch) as fixed factors; Sex and Trial Number were included as covariates in a subsequent step. There was a

[14] Face AOI is larger than the component parts which means that the overall proportional LT in higher, as there is more opportunity to interpolate gaps of missing data; See Appendix E for visualisation of this overestimation.

significant main effect of Age Point (F(2, 198)=4.96, p=.008, η_p^2=.047), with higher Prop LT to the face at 14 than 5 (p=.008, *CI*[.011 .094]) or 10 month groups (p=.044, *CI*[.001 .082]; Figure 3.7A). The effect of Age Point remained with Trial number and Sex included as covariates (F(2, 198)=3.96, p=.021, η^2=.040), and revealed a main effect of Trial Number (F(1,198)=5.85, p=.016, η_p^2=.029) and Sex (F(1,198)=10.9, p=.001, η_p^2=.053), which suggested that these variables affect LT values. There were no other significant main effects or interactions. With Language Experience added to the model, there was only a main effect of Age Point (F(2, 185)=4.88, p=.009, η_p^2=.050), which was maintained when accounting for covariates (p=.010, η_p^2=.051). There was no effect of Sex or Trial number nor a main effect of Language Experience. These results suggest that infants show an overall increase looking to the face stimulus with age, but this is not influenced by factors such as language of the stimulus or individual language experience.

3.13.1 Developmental and language-dependent changes in Eye and Mouth looking.

Next, Eye-to-Mouth ratios (LT to Eyes – LT to Mouth / LT to Eyes + LT to Mouth) were analysed with a LMM, looking at effects of Age Point, Language of stimulus and Language Experience within the sample. The first model returned a highly significant effect of Age Point (F(176)=116.9, p<.001, η_p^2=.57; Figure3.7B), with Sidak corrected pairwise comparisons showing higher ETM ratio at 5 than 10 months (*Mean Diff*=.653, *df*= 175, p<.001, *CI*[.516 .789]) or 14 months (*Mean Diff*=.911, *df*= 176, p<.001, *CI*[.757 1]). Additionally, ETM was significantly higher at 10 than 14 months (*Mean Diff*=.258, *df*= 176, p<.001, *CI*[.107 .410]). As positive values of the ETM represent more looking to the eyes, it is evident that infants were looking for longer at the eyes at 5 months, which was followed by an increasing gaze shift to the mouth at 10 and 14 months. There was no significant effect of Stimulus language nor an interaction with Age Point. Taking into account the covariates, the effect of

Age Point remained (p<.001, η_p^2=.59), and there was no significant effect of Sex (*Wald Z*=.709, p=.478) nor Trial number (*Wald Z*=.000, p=1).

With Language Experience added to the model, there was a main effect of Age Point (F(175)=71.03, p<.001, η_p^2=.28). However, there was no effect of Language Experience (F(61)=1.99, p=.163, η_p^2=.001), which suggested that English-only and ALE infants had similar ETM ratios. There was no significant effect of Stimulus language (F(162)=1.54, p=.216, η_p^2=.009) or any interaction terms of note. With Sex and Trial number added to the model, the effect of Age Point remained (p<.001, η_p^2=.27) as well as an added effect of Language Experience (F(8.6)=6.5, p=.032, η_p^2=.43). Pairwise comparisons showed lower ETM ratio (i.e. higher looking to Mouth AOI) in English-only than ALE group (*Mean Diff*=-.368, CI[-.697 -.040]). There was no effect of Stimulus language nor any other interaction terms. The co-variance parameters of Sex (*Wald Z*=-2.09, p=.036), whereby Females showed higher towards the mouth than Males (t(218)=-1.94, p=.051, r=0.13). Effect of Trial Number (*Wald Z*=-1.2, p=.23) was not significant.

Infant Peak looks to the Eyes vs. Mouth were then explored (Peak ETM= (Peak LT Eyes - Peak LT Mouth) / (Peak LT Eyes + Peak LT Mouth)). The model returned a significant effect of Age Point (F(191)=16.83, p<.001, η_p^2=.81). Fixed effects revealed that there was significantly higher Peak ETM at 5 than 10 (*Mean Diff*=.535, *df*=176, p<.001, *CI*[.405 .665]) and 14 months (*Mean Diff*=.77, *df*=177, p<.001, *CI*[.624 .916]). There is also a significantly higher Peak ETM at 10 than 14 months (*Mean Diff*=.235, *df*=177, p<.001, *CI*[.091 .378]); which indicated that infants focused longer on the mouth with increasing age. There was no main effect of Stimulus Language nor an interaction with Age Point. With covariates added, the effects of Age Point remained (p<.001, η_p^2=.8), and no significant effects Stimulus language, Sex or Trial number.

With Language Experience added to the model, only the main effect of Age Point on Peak ETM remained ($F(176)=58.24$, $p<.001$, $\eta_p^2=.39$). Additionally, there was a marginally significant Age Point x Language Experience interaction ($F(56.8)=2.94$, $p=.055$, $\eta_p^2=.095$). Follow-up *t*-test split by Age Point showed lower Peak ETM at 5 months in English-only than ALE group ($t(55)=-2.34$, $p=.023$, $r=.3$), i.e. longer Peak Look towards the eyes in 5-month ALE group, irrespective of the language of the stimulus (see Figure 3.7C). With covariates added, the effect of Age Point remained ($p<.001$, $\eta_p^2=.39$), and the Age Point x Language Experience interaction became significant ($p=.032$, $\eta_p^2=.11$). Neither Sex (*Wald Z*=1.64, $p=.101$) nor Trial Number (*Wald Z*=1.2, $p=.1$) were significant as covariate parameters in the model.

3.13.2 Individual stability of Eye-to-Mouth looking.

Next, I examined stability of ETM and Peak ETM within each individual participant over developmental time. There was a significant association between ETM at 5 and 10 months ($r(54)=.461$, $p<.001$, *CI*[0.22 0.64]) as well as at 10 and 14 months($r(40)=.589$, $p<.001$, *CI*[0.34 0.75]), which suggested that individual looking behaviour at an earlier testing age was predictive of looking behaviour at an older age. When partialled out for Stimulus Language and Language Experience, only associations between 10 and 14 months ETM ratio remained significant. Individual stability in Peak ETM responses was also significant, albeit reduced in strength, between 5 and 10 ($r(54)=.314$, $p=.021$, *CI*[0.05 0.53]) and 10 and 14 months ($r(40)=.316$, $p=.047$, *CI*[0.001 0.56]), which suggested that ETM looking time ratio may be a more stable measure than Peak look over time.

3.13.3 Behavioural comparisons.

The dependent variables, i.e. ETM and Peak ETM were compared for each Stimulus language to (1) subscales on the Expressive and Receptive Language scores on the Mullen scale at every Age Point and (2) Total number of Words Understood & Said on the CDI at 14

months, controlling for Age Point. There were no significant relationships between the ETM/ Peak ETM ratio and the behavioural metrics of language acquisition (all *p*s >.18).

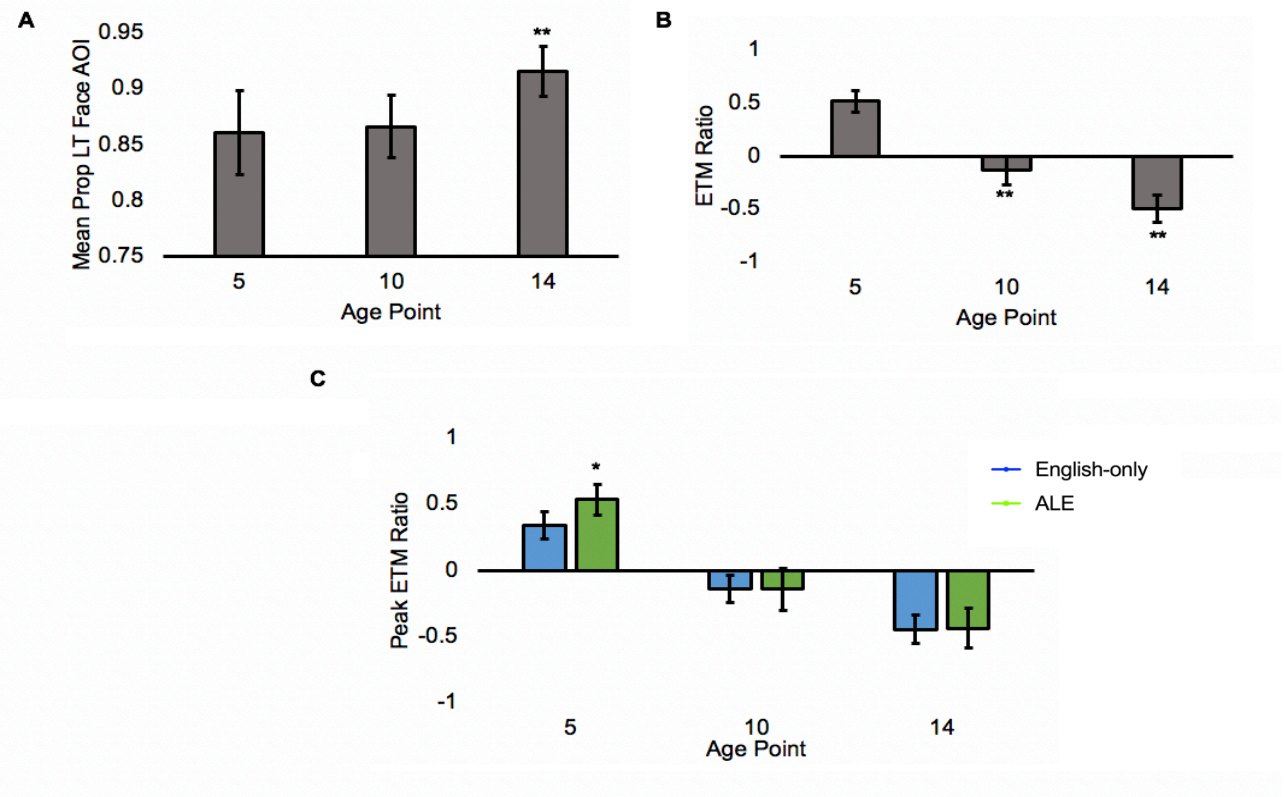

Figure 3.7 **(A)** Age comparisons of LT to Face show a significantly higher proportional LT to the face at 14 than 5 or 10 months **(B)** Age-related changes in ETM ratio, with gradual increase of looks towards the mouth with age and **(C)** pattern of differences in Peak ETM differences with language experience, infants with ALE showed higher looking towards the mouth at 5 months of age. Note. Average values represent estimated marginal means generated by the model. ** $p<.001$. Error bars represent 95% CI.

3.14 Discussion

The present study aimed to examine effects of age and language experience on individual developmental trajectories of selective attention in audiovisual speech perception. An attentional shift was observed away from the Eyes and towards the Mouth region between 5 and 14months of age, but no differences were revealed based on the language of the stimulus. There was also a marginal effect of individual language experience on selective attention, and these findings will be discussed and evaluated based on previous literature in the field.

3.14.1 Do infants show dynamic attentional shifts between the eyes and mouth over the first year of life?

Primarily, results of the selective attention task showed evidence of the first attentional shift towards the Mouth of the speaker between 5 and 10 months of age, which is thought to coincide with the onset of infants' spontaneous babbling. This was originally described by Lewkowicz & Hansen-Tift (2012), where the first shift was defined between 4 and 8 months. However, the second attentional shift back to the eyes was not observed (Barenholtz et al., 2016; Lewkowicz & Hansen-Tift, 2012) for native or non-native nursery rhymes between 10 and 14 months as hypothesised. Both Mean and Peak ETM ratios actually suggested that infants looked even longer to the Mouth of the speaker by 14 months, irrespective of the language of the stimulus (this is further explored in Appendix D, where the Prop LT to eyes and mouth were investigated separately over time to look at age-related changes).

Current observations of Peak looking time revealed increases in sustained attention towards the Mouth with age. Based on the assumption that attention towards the Mouth is essential towards language learning (Pons et al., 2015; Tenenbaum et al., 2015), isolating audiovisual information from a language they are in the process of learning rather than a completely unfamiliar language would accelerate this process. Present task highlights that the

secondary attentional switch may be protracted beyond 10 months of age, which warrants further experimental study. Interestingly, a steeper shift in Peak looks was found towards the Mouth in infants from English-only backgrounds, which suggested that infants in this group were attending to information from the mouth for longer than the ALE group.

3.14.2 Effect of native and non-native language in eye-to-mouth looking.

As there were no any significant effects of stimulus language, it is important to question the validity of the stimuli in the selective attention task in capturing native language specialisation in pre-verbal infants. On one hand, nursery rhymes were performed by a Dutch-English bilingual speaker where the tone and pitch of the songs were matched for both languages. Differences between native vs. non-native languages could therefore be attributed to familiarity rather than preference towards a particular speaker and/or song. It was observed that infants were equally engaged with stimuli of both languages, showing only the effect of age on looking time.

One potential explanation for equal engagement in native and non-native stimuli is that the speaker had an accent. Accented speakers have been found to impact many aspects of infant perception, including differential lateralisation of responses in the brain to accents, differences in phonological discrimination, rate of word learning and social preference (Jusczyk, 1985; Kinzler et al., 2009, 2012; Rost & McMurray, 2009; Sato et al., 2009). A more likely contributor, however, is the high salience of the visual stimulus. Specifically, the video stimuli included in this task featured songs matched in pitch and 'motherese' style that has been reported as highly engaging for infants and children (80-95% of looking time was focused on the face region for both Dutch and English videos). Therefore, infants may have been interested in the videos irrespective of linguistic content. Findings from the present task are further supported by the observation that typically developing infants are increasingly motivated to engage with social stimuli with age (Mundy, 2005).

3.14.3 Effect of language experience on eye and mouth looking.

Based on previous research, it was expected infants with additional language experience would look more towards the mouth of the speaker across all ages (Pons et al., 2015; Tsang et al., 2018); and that this would reflect higher cognitive load/attentional engagement in language processing. However, a different trend was observed in early looking behaviour in the present sample. Infants with ALE looked longer towards the Eyes at 5 months, with similar trends towards Mouth-looking as in infants from English-only backgrounds. This could be due to the smaller number of participants in the ALE group, although some robust effects were reported from looking time and pupil data for Task 1. It could be hypothesised that infants with ALE were more socially-motivated to engage with the stimuli at 5 months due to higher variability in the quality of communicative information they receive in the first months of life, yet this prediction was not supported within the older age groups. Findings from the selective attention task were similar to that of Mercure and colleagues (2018), who observed no difference in selective attention towards the Eye or Mouth regions between their monolingual and bilingual groups. Researchers did, however, find that bilingual infants showed increased looking time to the face, although this difference was not present in my study. The findings suggest that English-only infants did not show bigger shifts towards mouth looking than infants with ALE, showing similar levels of attentional engagement and learning. It should be noted that studies of infant 'bilingualism' do not tend to use strict guidelines for levels of language experience in the home environment (within both the quality or the amount of phonological experience). It appears that effects of language experience are only apparent in studies with strict criteria of daily/weekly experience or experience with only specific language combinations (i.e. Spanish-Catalan bilinguals; Sebastián-Gallés et al., 2012). Therefore, early variation in language experience may be less influential on selective attention processing than previously suggested (see Chapter 3.14).

Further, no associations were observed between Eye-to-Mouth looking and language ability on a behavioural level. This finding was in contrast to previous studies, which found that Expressive Language abilities were positively associated with Mouth looking (Tsang et al., 2018; Young et al., 2009). Kushnerenko and colleagues (2013) reported that less efficient audio-visual matching of information from the mouth was associated with poorer receptive language ability at 14-18 months, which was supported by an additional EEG experiment (Kushnerenko et al., 2013). Further research is needed to establish more direct pathways between mouth looking and language production in early childhood (i.e. by observing mouth movements of the infants).

In conclusion, results from the selective attention task revealed some evidence to support age-dependent shifts in selective attention during speech perception across early infancy. While an increase in attention towards the Mouth with age was observed, this relationship was not affected by the language of the stimulus. At present, there are reservations over the specificity of the ETM and Peak ETM in indexing phenotypic expression of communicative ability and specialisation to native language. Nonetheless, three experiments outlined in this chapter featured a single group of infants followed longitudinally across early infancy, which adds an important dimension to the field dominated by cross-sectional paradigms.

3.15 Eye Tracking Tasks Summary

Taken together, the three experiments were used to measure infant processing of speech and language input from their environment over the first years of life. However, the was no robust evidence to support previous findings of increasing preference towards the native language and audiovisual integration occurring in typical development. The gaze metrics selected were not sensitive to individual differences in language experience or stimulus language. There was also poor individual consistency in performance on these tasks on an

individual level. Findings from these investigations question effects reported in previous literature and suggest that infant performance may be influenced by task demands or study design/analysis pipeline. The following section argued that the behavioural indices from the three experiments described in this chapter do not show strong evidence for experience-dependent specialisation or the active role of child-directed experience in typical development. Further, the external validity of infant eye tracking literature is questioned, which calls for further investigation of EEG-based markers of specialisation and individual communication ability as well as atypical development in the later parts of this thesis (Chapters 4-6).

The present set of studies did reveal age-related changes in looking behaviour towards socially-motivating stimuli. Although infants did not 'choose' to look at native over non-native language stimuli in Task 1, changes in looking time and pupil dilation suggested there were notable differences in processing of incoming social information based on age and language of the stimulus. These metrics further differentiated between infants with additional language experience in their home environment (i.e. increased pupil dilation towards English videos to suggested higher cognitive processing relative to the English-only group). However, the conclusions from the ALE group may be underpowered due to small sample size.

Present findings further highlighted the importance of individual variability in early language across infants with typical development. In the recruited sample, infants' ability ranged from 20-80 on Expressive Language and 30-75 on Receptive Language *t*-scores on the Mullen scale. Infant verbal production, i.e. number of words understood and said at 14 months ranged from 0 to over 160 words measured by the CDI, demonstrating the true variability in neurotypical infants without history of language disorders. Importantly, Tasks 1 and 2 described above did not show individual stability across Age Point. Future work would require repetition of the task within an age point, in order to examine test-retest reliability of individual gaze measures.

Findings from the eye tracking experiments revealed several inconsistencies with the existent literature on preverbal speech perception. These included the predictions of preference for native relative to non-native languages in Task 1, spontaneous audiovisual integration in Task 2, as well as bidirectional age and language dependent shifts in attention between eyes and mouth as an index of acquisition of phonetic categories in Task 3. It can be argued that inconsistencies with previous literature was due to task differences, where absence of training periods or exclusion of data based on predetermined criteria in other investigations. It is therefore important to note that there was no active 'preference' for native than non-native speech, as infants on the whole appeared to be equally engaged with the stimuli irrespective of the language presented. These discrepancies can also be explained by infant driven factors such as engagement or motivation (Figure 3.5), which was considerably difficult to control within the infant population.

Another point of consideration when evaluating these results concerns the ALE group. Infants in this group were rated by parents/caregivers as having variable levels of exposure to a second language in their home environment (30-70%) and are not classified as bilingual for the purposes of this investigation due to complexities in assessment of infant bilingualism (Byers-Heinlein, 2015). Due to the lack of objective measures of exposure to different languages (i.e. through recording of auditory environment of the child for a meaningful period of time), parent estimations were used to group infants. As previously argued, parent-report measures may not be accurate or consistent over time (Liu & Kager, 2017).

However, findings from this set of experiments may be used as proof of principle that the effect of exposure to more than one language can impact various aspects of early communicative behaviour. There were differences in the ALE group in pupil size responses and looking time (Tasks 1 and 3), although larger sample sizes are warranted in order to make conclusions about the effects of multiple language exposure. The three tasks above further

highlighted the need for a quantifiable metric of language experience that will correspond to later parent-reports of exposure in bilingual children (Gutiérrez–Clellen & Kreiter, 2003; Hoff et al., 2012). This will help us elucidate the links between amount of early experience and degree of native-language specialisation across developmental time using the tasks described above.

An important conclusion from this chapter is that current literature on infant speech perception may lack external reliability, and thus results should be interpreted with caution. This is particularly true in the case of critical periods, where chronological age is used as a predictor of certain abilities, without consideration of individual variability in brain development. It appears that in isolation, eye tracking is unlikely to provide a sensitive measure of infant communication development, which motivated the use of EEG to look at age-dependent changes in the brain.

3.15.1 Isolating behavioural predictors of specialisation.

Based on the results of the tasks above, the following dependent variables were selected as putative indices of experience-based specialisation (Table 3.5). These indices were used in dimensional analyses with data from EEG study that was run on the same population of infants at 5 and 10-month visits (see Chapter 4.5). It should be noted, however, that due to absence of robust effects of stimulus language or individual language experience, indices from eye tracking metrics alone are not sufficient predictors of specialisation and I therefore the focus of this work was shifted towards identifying EEG-markers of passive auditory processing of individual differences across typical and atypical development.

Table 3.7 *Summary of findings and eye tracking indices used for further comparison with EEG-data in Chapter 4.*

	Age/language-related changes	**Individual stability**	**Relation to phenotype**	**Included in further analyses?**
Task 1- Active Seeking	• No difference in stimulus choice • Differences in Prop LT to English only • Age Point, Condition and Language-Experience effects on PD	• Reaction time between 5 and 10 months • Pupil dilation between 10 and 14 months	• No significant associations found	1) LT native/non-native language 2) Pupil dilation for English and Italian stimuli
Task 2 – Audio-visual integration	• No differences in audiovisual matching with Age Point, Condition or Language Experience • Decrease in attentional engagement with stimuli over time	• No individual consistency found across dependent variables	• No significant associations found	N/A
Task 3 – Selective attention between eyes and mouth	• Attentional shift from the eyes to the mouth between 5 and 10 months • Increased looking to the eyes in ALE infants at 5 months	• Significant associations between peak and mean looking time between 5-10 and 10-14 months	• No significant associations found	1) Eye-to-Mouth ratio for English and Dutch stimuli

Chapter 4. Perception of vowel habituation and change and language development in infants with typical development and Neurofibromatosis

In the following chapter, I examined auditory habituation and change detection as basic neurophysiological markers of early brain specialisation. Both habituation and oddball paradigms have been used extensively in infant research. I assessed sensitivity of these EEG metrics to age-related changes, as well as investigated any atypicalities in auditory responses in infants diagnosed with Neurofibromatosis Type 1. NF1 is a genetic disorder characterised by atypical function of GABA neurotransmitter associated with inhibitory regulation of activity in the brain (Costa & Silva, 2002; Violante et al., 2013) with language and social communication difficulties reported from childhood and onwards (Dilts et al., 1996; Shruti Garg et al., 2015). The chapter marks the beginning of three separate studies of neural correlates of auditory processing, as the attempts to measure changes in behavioural specialisation with age and native language through eye tracking did not yield convincing results.

4.1 EEG Task 1: Age-Related Changes in Processing of Speech Sounds in Infants with Typical Development and NF1

This task has been included in a pre-registration document titled *"Auditory processing and language development in infants with Neurofibromatosis Type 1"*, submitted internally on 23/06/2019 (see Appendix G for copy of the document). Note there are a few differences between this document and the present chapter (including regions of interest chosen and additional analysis techniques including oscillatory power). Differences between analytic pipelines used in present chapter and the internal pre-registration document were largely due

to the exploratory nature of the task, with different aspects of the EEG signal examined in future publications.

One of the most important functions of the human brain is the ability to recognise and differentiate between novel and familiar information, and treat it accordingly. Repeated stimuli, for example, receive less processing with every repetition in what is known as habituation. On the other hand, infrequent or novel stimuli elicit an enhanced neural response, termed change detection or novelty preference. Habituation and change detection may be useful as potential indices of specialisation, as brain responses have been reported to become increasingly more localised and increase in amplitude with age (Ghislaine Dehaene-Lambertz, 2000; Turk-Browne et al., 2008).

In infant literature, the habituation paradigm has been used to (1) measure the learning capacity of the infant and (2) assess their capacity to discriminate novelty by introducing a novel stimulus after habituation has taken place. The strength of the habituation response has further been used to predict future cognitive abilities of the infant (McCall, 1979; McCall & Carriger, 1993), as well as neurodevelopmental conditions such as ASD (Guiraud et al., 2011; Linke et al., 2018). Habituation has thus been put forward as a measure of cortical efficiency – the speed with which the brain analyses external stimuli, which has downstream effects onto processing of complex information such as faces and language. The paradigm has been extensively investigated in the auditory modality due to ease of administration across different levels of verbal and cognitive abilities. Previous studies report habituation as a robust phenomenon to study auditory perception across the lifespan, from maturation of the central nervous system in foetal brain development (Muenssinger, Matuz, et al., 2013) to the aging process of the brain between childhood and late adulthood (Paul et al., 2005).

There are two important methodological advantages to using auditory rather than visual habituation paradigms. Firstly, auditory habituation studies are less likely to be affected age-

dependent effects on looking behaviour prevalent in visual paradigms (Turk-Browne et al., 2008). Younger infants, for example, are more likely to look at familiar stimuli and older infants would orient towards novelty. Additionally, there is difficulty in selecting appropriate complexity of visual stimuli to capture habituation accurately – i.e. simple 'light flashes' may be less likely to capture attention, while complex visual scenes will require more trial repetitions. On the other hand, auditory habituation stimuli can be administered while the infant is engaged in a silent play activity and does not require for them to focus on the screen. There is comprehensive understanding of how auditory processing occurs in the infant brain with evidence across many different types of paradigms (Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002; Kushnerenko et al., 2007; Risto Näätänen et al., 2007; Turk-Browne et al., 2008).

There are several methods for measuring auditory perception in early infancy. Behavioural techniques such as looking time have been used in the past (Chapter 3.1), although an indirect metric of cognitive processing, produces small amounts of data and often requires active attention from the infant (Chen et al., 2016). Using electrophysiological brain responses from Event-Related Potentials (ERPs) produces much larger volumes of data, and is therefore the most common tool for investigating early auditory processes in infancy (Ghislaine Dehaene-Lambertz & Baillet, 1998; He, Hotson, & Trainor, 2007; Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002). EEG may therefore be useful as an additional tool to look at early brain specialisation, by tapping into auditory processing changes rather than age-related differences in the behavioural phenotype assessed in the chapter above (see Chapter 2.2.1 for further advantages and limitations of the EEG method).

4.1.1 Auditory habituation.

The most common hypothesis regarding habituation and brain maturation, is that the rapidity of the response increases with age, reflecting an increase in an older infant's processing

ability versus a neonate. Specifically, the older an infant, the quicker they should habituate to repeated auditory input as a result of the increases in brain maturation. First consistent evidence of age-related change in habituation was recorded through visual fixation (Lewis et al., 1969) and heart rate changes (Berg, 1974; Brown, Leavitt, & Graham, 1977), although the direction of habituation response is difficult to interpret as both increases and decreases in habituation were reported across different stimulus types.

Event-related potentials to auditory stimuli have shown decreases in amplitude of neural responses following repetition of standard stimuli (Dehaene-Lambertz & Baillet, 1998; Muenssinger, Matuz, et al., 2013; Nordt, Hoehl, & Weigelt, 2016). However, the pattern of auditory ERP peaks is very complex in early development. Kushnerenko and colleagues (2002) examined developmental changes in auditory responses and showed that P1 amplitude increased between birth and 3 months, and remained stable between three months to a year, while the N2 became more negative between 3 and 9 months of age. It was evident that differences in ERP responses are highly specific to age and stimulus, as well as the temporal/spatial region of interest (ROI) selected for analysis. Chen and colleagues (2016; Figure 4.1) found that auditory responses to repetition become better time locked with age (i.e. decreased amplitude P1 and N2 responses between 4 and 12 months of age across left and right frontal regions). They further reported decreases in latency of neural response with age, which suggested increased specialisation towards segmentation and processing of incoming auditory information.

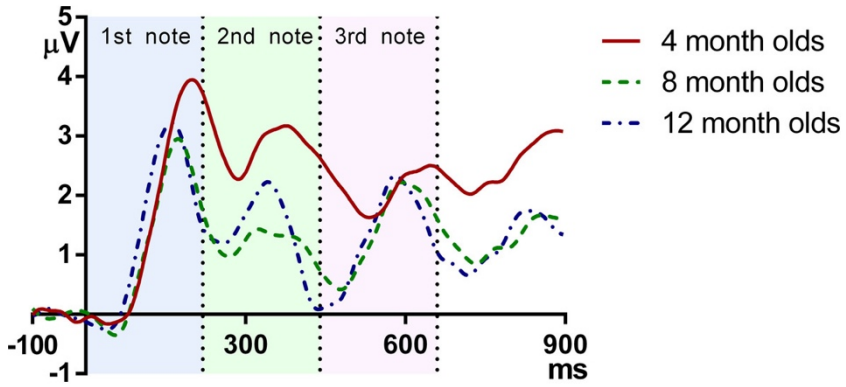

Figure 4.1 Grand average responses to three standard tones in three age groups. P1 component showed the biggest reduction between Standard 1 and Standard 2 across all age groups. Retrieved from Chen et al. (2016).

4.1.2 Auditory change.

Stronger brain responses have been reported in response to novel stimuli (Benasich & Tallal, 1996; Cheour, Leppänen, & Kraus, 2000; Sambeth, Huotilainen, Kushnerenko, Fellman, & Pihko, 2006). In ERP research, change detection has been characterised by the mismatch negativity response – which is a component of the ERP in response to a deviant stimulus (MMN; (He et al., 2007; Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002)). The MMN is elicited when a deviant tone is presented in a sequence of repeated standards, a negative peak appearing between 130-250ms after stimulus onset (see Figure 4.2). In infants, Alho and colleagues (1990) recorded the first MMN, which has since been extensively studied in young populations using pure tones and frequency modulation (for a summary see He et al., 2007). He and colleagues (2007) found that 2-4 month olds all showed different responses to deviant versus standard tones, although the response was dominated by a slow positive wave at 2 months, with an adult like MMN appearing around 3-4 months.

The MMN is thought to reflect the brain's automatic change detection process. The emerging discriminative ability has also been shown to be sensitive to the type of stimuli presented. Infants were found to be sensitive to both pitch (Fernald & Kuhl, 1987; He et al.,

2007; Werker & McLeod, 1989) and frequency changes (Bishop, Hardiman, et al., 2011; Olsho et al., 1982). It has been argued further that better auditory discrimination abilities facilitate learning of vowel categories (Bosch & Sebastián-Gallés, 1997; Trainor & Desjardins, 2002) and help distinguish lexical and grammatical boundaries, which is a pre-requisite for the acquisition of spoken language (Jusczyk & Derrah, 1987; Weber et al., 2004; Werker & Yeung, 2005). Additionally, behavioural studies have shown a rapid increase in infant's discrimination of frequencies between birth and 4 months of age., although they do not reach adult-like levels of proficiency until later in childhood (Olsho, Koch, & Halpin, 1987; Olsho, Koch, Halpin, & Carter, 1987). Note that in the present task, the Deviant stimuli are presented at the end of each auditory train with a 50% probability. It is likely that due to the increased number of deviant trials, a more distinct change detection response would be observed within the ERP waveform (Guiraud et al., 2011; Rivera-Gaxiola et al., 2005).

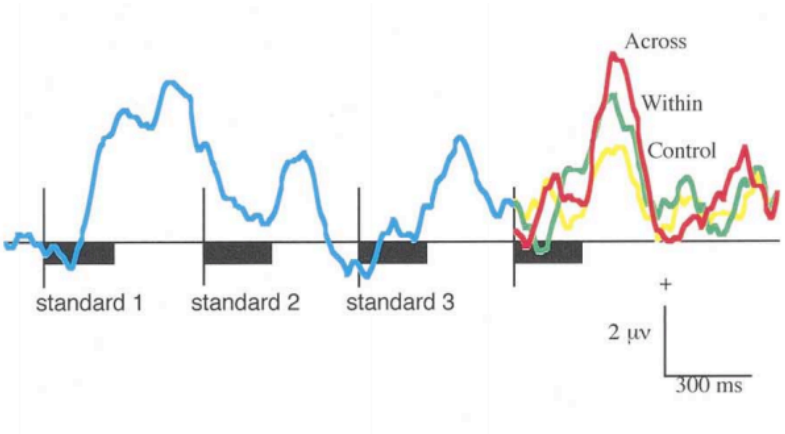

Figure 4.2 Grand averaged responses showing a decrease in response following repetition of standard tones (blue line) as well as recovery after syllable change (red and green lines). Reprinted from Dehaene-Lambertz & Baillet (1998 - Figure 1A).

4.1.3 Age-dependent changes.

Next, previous literature on age-dependent effects on repetition and change processing were considered. A longitudinal study by Edgar and colleagues (2015) reported age-related differences in amplitude of P2 and N2 components, as well as lateralisation of the MMN response between 6 months and five years in response to auditory paradigms. The researchers proposed that increase in myelination with age facilitated increase in speed of auditory processing. Conboy and colleagues also reported that discrimination of native and non-native phonemes changed over the first year of life (Conboy et al., 2008; Rivera-Gaxiola et al., 2005). However, there is still limited evidence on how habituation and change detection mechanisms emerge in typical and atypical development. This is further complicated by two potential explanations of change detection, i.e. mismatch response can be used to (1) index discrimination ability or (2) detect general sensitivity to change between presented stimuli. The second implication is associated with habituation response, as failure to detect change is interdependent with a reduced response following repetition. For the purposes of this work, change detection was regarded as a general sensitivity to change (thus comparisons are run between Standard 3 and Deviants, rather than the sum of Standard tones).

Prospective designs have been used to test whether early ERPs have predictive outcome for early language development (indexed by scores on the MacArthur-Bates Communicative Development Inventory, CDI; Fenson et al., 2007). The CDI was commonly used in the study of responses to native vs. non-native language contrasts, where infants who showed higher P150 response were also reported to produce more words than infants who showed larger N2 (250-500ms) responses to the non-native sound contrast (Rivera-Gaxiola et al., 2005). Kuhl and colleagues (2006) recorded ERPs in infants at 7-8 months of age and collected CDI reports from parents at several time points between 14 months 28 months (2.5 years). Mismatch responses calculated for the native/non-native language contrasts (300-600ms post stimulus

onset) showed that greater negativity to the native contrast was subsequently correlated with greater total number of words produced at 18 and 24 months. In addition, degree of the MMN response was related to parent-rated sentence complexity at 24 months, while greater non-native contrast was associated with fewer words at 24 months and reduced rate of growth between 14 and 30 months of age (Kuhl et al., 2006; Kuhl et al., 2008).

However, there is low consistency across studies in response to both simple tones and phonetic stimuli, with studies showing both negative (Alho et al., 1990; Leppänen, Eklund, & Lyytinen, 1997; Trainor, Samuel, Desjardins, & Sonnadara, 2001) and positive (Dehaene-Lambertz & Dehaene, 1994; Leppänen et al., 2004; Trainor & Unrau, 2012) mismatch responses. There is also considerable variability in amplitude and latency of responses across individuals (Cheour et al., 1998; Kushnerenko et al., 2002). Interpretation of reported data should therefore be taken with caution.

4.1.4 Atypicalities in early auditory processing.

Habituation and change detection of auditory stimuli have also been investigated as a potential causal mechanism of atypical sensory perception and socio-communicative difficulties in children diagnosed with Autism Spectrum Disorder (Guiraud et al., 2011; Linke et al., 2018; A. Seery et al., 2014) and their first-degree relatives (Rojas et al., 2011; Uljarević et al., 2014). Dysregulation within this process has been associated with atypical behaviours in response to sensory stimuli, where both hyper- and hypo-responsivity have been reported in perception of auditory information (Wing, 2003).

Kemner and colleagues (2002) reported atypical habituation of a P50 component in infants with later ASD. Specifically, there was a lack response suppression following stimulus repetition. Further, presentation of short auditory bursts has shown sensitivity to children with poor language outcome, including elevated likelihood of developing a language disorder

(Benasich & Tallal, 2002; Choudhury, Leppanen, Leevers, & Benasich, 2007). Reduced habituation (i.e. lack of reduction of ERP response following repetition, no enhancement following deviant tones) was also observed in infants with elevated familial likelihood of ASD than those with no family history of the disorder (Guiraud et al., 2011). Infants with an elevated familial likelihood of ASD showed no difference between responses to the Standard tone versus a Pitch deviant, but did show some sensitivity towards white noise (typically used as a control as it evokes strong responses in hearing individuals). The results suggested that while infants with elevated likelihood of ASD has similar hearing thresholds, they were not detecting change in more subtle aspects of sound, i.e. pitch. As the sample in this study was based on family history rather than developmental outcome of the participants, atypical habituation was proposed as a brain mechanism present in the broader ASD phenotype. Authors also noted reduced responses to auditory change, as infants with familial history of ASD did not show differences in responses between standard and noise stimuli (Figure 4.3).

Atypical habituation responses have also been noted in other childhood-onset neurodevelopmental and genetic disorders, including Schizophrenia, Fragile X and Williams Syndrome (Ethridge et al., 2016; Grice et al., 2003; Johannesen et al., 2005; Vivanti et al., 2018). Ethridge and colleagues (2016) reported that habituation was atypical in adolescents and adults with Fragile X, a genetic disorder with elevated incidence of ASD (Ethridge et al., 2016; Grice et al., 2003; Johannesen et al., 2005). Both reduced suppression of the N1 and increased gamma power (oscillatory response associated with perceptual binding) were found in response to tone repetition, which were subsequently associated with infant's sensory behaviour and socio-communicative skills. These findings suggested that simple auditory tasks can be used to show sensitivity to group differences (i.e. typical development versus individuals diagnosed with Fragile X) and behavioural phenotypes.

Based on the evidence, development of habituation and change detection responses was studied in populations of infants with Neurofibromatosis Type 1 (see Chapter 1.6.2.1 for details of this rare genetic condition and summary of current research). Although the physical phenotype of NF1 may include neurofibromas, café-au-lait macules, Lisch nodules and abnormalities within the skeleton and the central nervous system (Jett & Friedman, 2010), the main challenges reported by parents and children with NF1 in clinical settings are cognitive, social and behavioural difficulties (Hyman et al., 2005). Indeed, there is increased incidence of ASD and other neurodevelopmental conditions associated with the condition (Brei, Klein-Tasman, Schwarz, & Casnar, 2014; Garg et al., 2013b). NF1 is not associated with profound developmental delays, but rather with a more subtle shift in IQ (Hyman et al., 2005). Due to this, comparisons with typically developing infants are less confounded by selection bias and developmental challenges within the NF1 group (Aylward, 2002). The underlying hypothesis of syndromic ASD studies is that there is a finite number of common mechanisms and molecular pathways in ASD that can be used as intervention targets. Yet no treatments or practical targets have been identified, specifically within the developing sample. Based on research outlined above, auditory habituation and change detection appear as two potential processes that may be disturbed across several developmental and genetic disorders, as well as individuals with broader idiopathic ASD, and therefore reflect an underlying failure to encode basic perpetual information (Fenckova et al., 2019; Guiraud et al., 2011; Jones, Dawson, Kelly, Estes, & Webb, 2017; Knoth et al., 2018).

A recent study by Fenckova and colleagues (2019) identified a further 93 genes that play a role in habituation learning, which converge on the Ras-MAPK pathway. As NF1 is considered the most common of 'RASopathies', i.e. developmental syndromes with mutations in genes that encode protein components of the RAS-MAPK pathway (Tidyman & Rauen, 2009), it can be hypothesised that there are important insights to be gained from investigating

habituation as a mechanism of dysregulated specialisation in this unique population. To date, there have not been any studies to describe habituation or change detection responses in individuals with NF1, although one investigation with children and adolescents with NF1 is currently ongoing (Lancette et al., 2018).

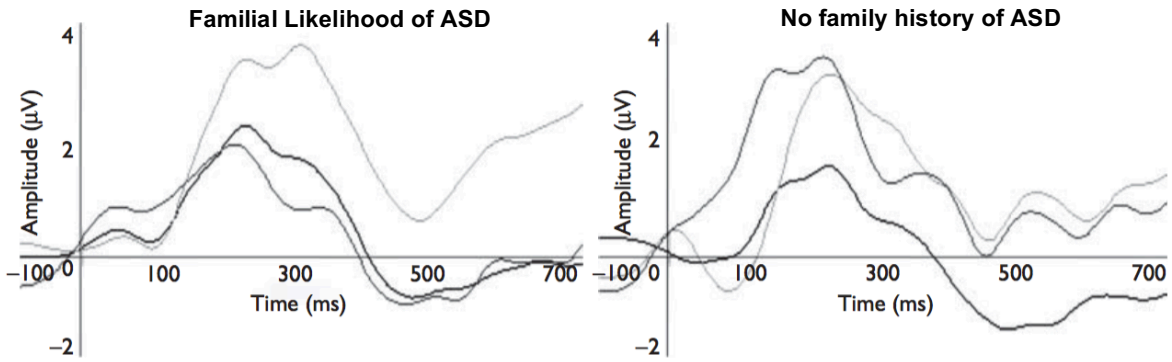

Figure 4.3 ERP responses to a sum of Standard tones (Black line), tone deviants (Dark-grey line) and noise stimuli (Light-grey). Note the positive peak 100-300ms and the subsequent negativity 300ms+. Adapted from Guiraud et al. (2011).

An important question regarding speech perception in early typical and atypical developmental pathways is whether a basic auditory task, often based on non-verbal stimuli, can be used to predict later language acquisition (Conboy et al., 2008). While many studies propose links between domains of language learning and word acquisition (Houston & Jusczyk, 2003; MacNeilage & Davis, 2000; Werker & Yeung, 2005), fewer have looked at the links between early perceptual abilities and language outcomes. Molfese and colleagues conducted a retrospective analysis of ERP recordings in response to syllables in neonates, which was associated with measures of language comprehension at 3, 5 and 8 years, as well as reading ability at 8 years of age (Molfese, 2000; Molfese et al., 1999; Molfese & Molfese, 1985). They found that the 'maturation' of the ERP response (i.e. slope, acceleration of growth in the N1 specifically) to both speech and non-speech stimuli between ages 1-8 years was related to reading difficulties at 8 years (Espy et al., 2004). The classic MMN response has also

been used to predict outcome in children with elevated likelihood of dyslexia (Zuijen et al., 2013).

Taken together, infant EEG studies may provide important insights into early processing of auditory information and how it contributes to the emergence of language-related skills in diverse developmental trajectories. The experiment described below is the first analysis of data comparing cohorts of typically developing infants to those with a diagnosis of NF1.

4.1.5 Present study.

In the present task, I examined age-related changes in auditory habituation and change detection responses using an 'auditory trains task' (adapted and simplified from the auditory oddball paradigm from Dehaene-Lambertz & Baillet (1998; Figure 4.1) and Guiraud et al. (2011)) in infants with typical development (TD) and those diagnosed with Neurofibromatosis Type 1 (NF1).

The paradigm was selected for several reasons. Traditional 'oddball' tasks are highly dependent on attentional engagement in order to form probability structures for repetition and change within the presented stimuli. As the infants with NF1 have not been investigated prior to this study, there may be group differences in attentional engagement relative to typically developing peers. Simplifying the stimuli into a pattern of four reduces the cognitive demands of the task, as the probability structure of the set of four stimuli can be easily processed even if attentional engagement is low. McDiarmid and colleagues (2019) argued that habituation is a complex response with many potential interacting mechanisms, which means that presentation of a simple, predictable stimulus should in theory provide robust habituation and change detection responses. The current paradigm thus taps into the basic elements of auditory processing (relative to auditory oddball paradigms, which can be used to index both low and

high-level processing). Although this means that it is not possible to compare results from this task directly to the traditional MMN designs, it is useful in unique and understudied populations such as NF1. Further, the auditory trains paradigm allowed to administer more comparable trial numbers for all conditions, as deviant tones occurred at the end of each 'train' of vowels (whereas MMN frequently uses 85% standards vs. 15% deviant tones), which is important when working with more challenging infant populations.

Within the auditory train paradigm, it was predicted that infants with no family history of genetic or developmental disorders would show the expected habituation response following repetition of Standard tones. Additionally, an increase in amplitude of the ERP response was expected between the last Standard and the two deviant vowel conditions (Pitch Deviant, Vowel Deviant), to indicate change detection. It was further predicted that the ERP response to Vowel deviant will be stronger at 10 months of age (i.e. biggest amplitude increase), to reflect increased language processing ability. In infants with NF1, a reduced habituation response was expected, i.e. no differences in amplitude between Standard tones. Further, reduced/absent increase of ERP amplitude to Deviant tones was expected, which would indicate early sensory processing difficulties in this population. As deviant tones were presented consistently at the end of each auditory train (see Figure 4.4), it was expected that there may be some 'preparatory' responses (i.e. recovery of the habituation response between Standard 2 and Standard 3) in the older age group, as reported in previous literature (De Boysson-Bardies, Halle, Sagart, & Durand, 1989; Kuhl & Meltzoff, 1996; Patterson & Werker, 1999). Next, an association was expected between the strength of the habituation response (i.e. difference between Standard 1-2, Standard 3 and Deviant Pitch/ Vowel) and scores on the Receptive and Expressive Language subscales on the Mullen (Mullen, 1995), irrespective of group status. Further, the relationship between individual habituation and change detection responses and scores on the CDI at 14 months of age (Fenson et al., 2007) was investigated.

4.2 Methods

4.2.1 Participants.

For this task, 52 typically developing (TD) infants were recruited as part of the GABBLES cohort; see Chapter 3.2.1 for details). At the 5-month visit (age *M*= 5mo15d, *SD*= 9d), 49 attended the laboratory and 45 took part in the EEG protocol. Note that four infants did not take part in EEG due to tiredness. At 10 months (age *M*=10mo6d, *SD*= 8d), 48 infants attended the visit, providing 46 EEG recordings (1 missing due to tiredness and 1 due to intolerance of the net). In order to match the NF1 cohort, EEG data from the GABBLES cohort will be discussed only from the 5 and 10-month but not the 14-month visit. No family history of genetic or neurodevelopmental disorders was reported.

In addition, 30 infants with a clinical diagnosis of NF1 were recruited through local and genetic centres as part of the Early DEvelopment in NF1 (EDEN) study[15]. All participants had their diagnosis confirmed via molecular testing of cord blood samples or clinical diagnosis based on National Institute of Health (NIH) consensus criteria and had no other developmental concerns at the time of the visits. All of the infants recruited for the study were from English speaking households. At the 5-month time point (age *M*=6mo3d, *SD*=16.8d), 13 infants attended the laboratory visit and 13 took part in the EEG protocol, while at the 10-months visit (age *M*= 10mo7d, *SD*=16.3d), 22 infants attended and 16 completed the EEG protocol. Note that differences between numbers initially recruited for the study and the final number of EEG recordings are due to (1) non-compliance with EEG protocol, (2) equipment failure or (3) differences in experimental protocols (4 of the NF1 infants took part in a pilot study, of which

[15] Note that the 14 month visit of this group will also be included in analysis in Chapter 7.

the EEG was not included as part of the experimental protocol). Moreover, there are fewer infants recruited before the 5-month visit due to delay with families receiving the diagnosis (expert consultation take longer to be scheduled and attended and genetic testing is not routine procedure at present).

Finally, 32 (71.1%) of the 5-month and 38 (82.6%) of the 10-month TD infants from the GABBLES cohort provided usable data. From the EDEN cohort, nine infants with NF1 (69.2%) provided data at the 5-month and 16 (100%) at the 10-months visit. For breakdown of initial recruitment numbers and final samples of "good" data, see Table 4.1. As the EDEN study is currently ongoing, there is no outcome information available at present for these infants (such as a later diagnosis of ASD, ADHD or Developmental Delay).

4.2.2 Stimuli.

The auditory trains task consisted of sounds originally designed by Guiraud et al. (2011). Each train was composed of four consecutive 50ms sounds with a 5ms rise and fall time. The first three sounds in each train were frequent Standards, and the fourth was an infrequent Deviant. Standard sounds were all a /u/ vowel sound administered at 500Hz (Figure 4.4). Deviants were either a Deviant Pitch (/U/ sound administered at 650Hz) or Vowel sound (/i/ sound administered at 500Hz) with 50% probability each. The inter-stimulus interval (ISI) was set to 500ms, and the inter-train-interval was a jittered between 3000-5000ms. The sound intensity was 70dB SPL. The sounds were presented for between 7 and 10 minutes, or until the infant became restless (Table 4.1). The higher number of total trials retained in the NF1 group at 10 months relative to the TD infants at the same time point may be due to reduced mobility and increased likelihood of infants with NF1 to sit through the whole protocol. Following Guiraud and colleagues (2011), Kolesnik and colleagues (2019), as well as the *a priori* hypotheses, responses to Standards 1, 2 and 3 were compared in a Habituation analysis; while Standard 3 is compared to Pitch and Vowel change deviants in analysis of change detection, as stronger

change detection responses have been reported between the last repetition of the common standard tone versus the first deviant (Todd et al., 2014).

4.2.3 Procedure.

The auditory trains task was administered at the end of a battery of visual EEG tasks. Infants were seated on their parents/caregiver's lap facing the experimenter in a sound attenuated room with sounds presented from two speakers located on the screen, 1 metre apart and located 1 metre away from the infant. Infants engaged in silent play (toys and/or bubbles) with a researcher, which kept them calm and engaged. Note that the task was still administered if the infant fell asleep in the first part of the EEG protocol. The data was retained for the final analysis as similar response strengths have been reported in sleeping infants in similar paradigms (Colrain & Campbell, 2007; McNamara et al., 1999). Additionally, the Mullen Scales of Early Learning (MSEL; Mullen, 1995) were administered in the standard format, with assessments for both cohorts carried out by a small team of trained experimenters. Parents were also asked to complete a set of questionnaires at home within two weeks of the test date, which included the Infant Behaviour Questionnaire-Revised (IBQ-R; Enlow, White, Hails, Cabrera, & Wright, 2016; Putnam, Helbig, Gartstein, Rothbart, & Leerkes, 2014) at 5 and 10 months; as well as the Communication Development Inventory (CDI; Fenson et al., 2007) at 14 months.

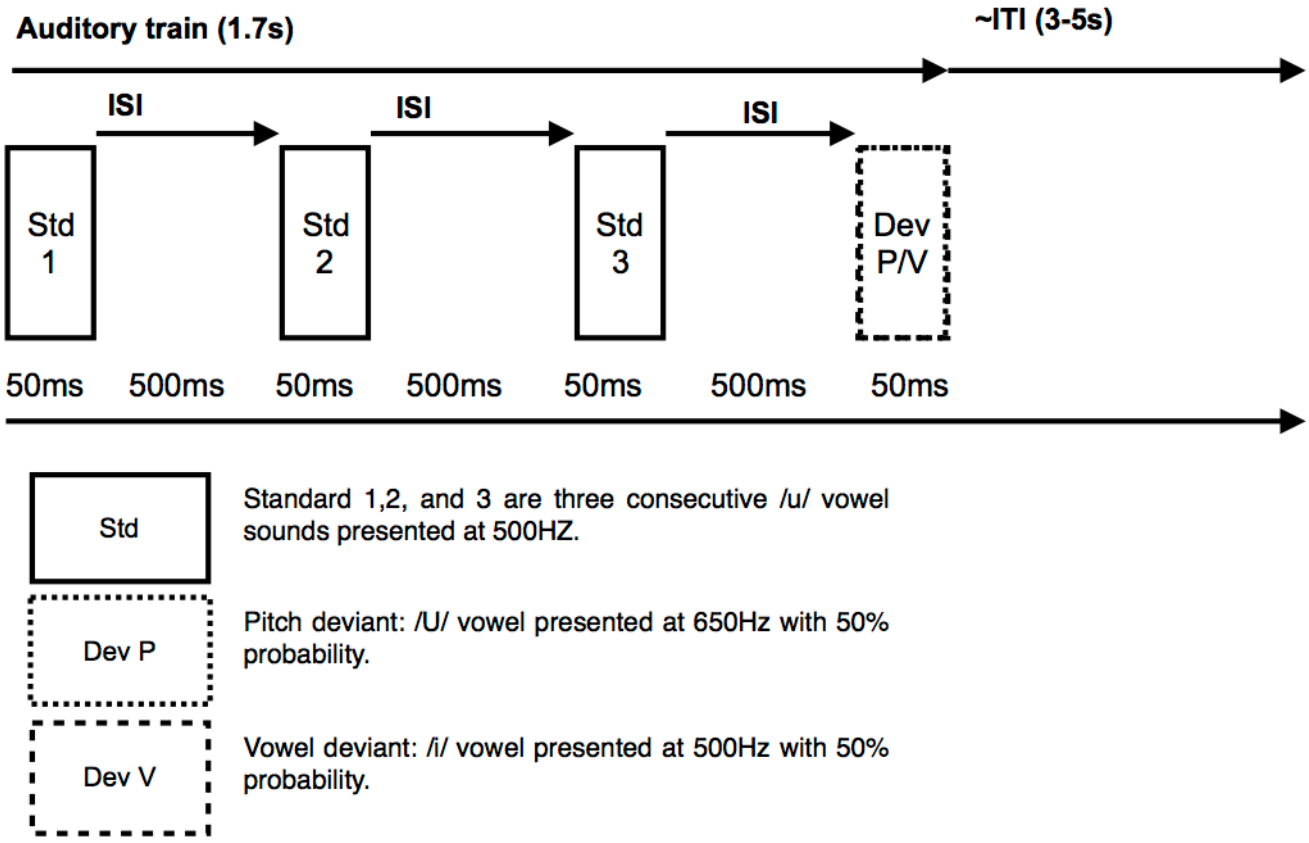

Figure 4.4 Auditory trains paradigm – vowel sound stimuli adapted from Guiraud and colleagues (2011). Original 'trains' design has been adapted and simplified from Dehaene-Lambets & Baillet (1998) and Karhu and colleagues (1997). The ISI was set at 500ms between each stimulus presentation and the ITI was jittered between 3-5s.

Table 4.1 *Summary of the total sample and number of "good" datasets used in the final analysis for auditory trains task.*

	Group	Total Trials Retained (Administered)	Standard (/u/ Vowel at 500Hz)			Vowel Deviant (/i/ Vowel at 500 Hz)	Pitch Deviant (/u/ Vowel at 650 Hz)
			STD1	*STD2*	*STD3*	*VowDev*	*PitDev*
5 months	*TD (n =32)*	*196.15* (343.15)	44.72 (*SD*=18.8, 22-10)	49.4 (*SD*=21.3, 22-110)	49.7 (*SD*=18.9, 25-101)	25.1 (*SD=10.1, 11-52)*	26 (*SD=10.1, 10-48)*
	NF1 (n= 9)	*222.85* (325.63)	50.8 (*SD*=20.1, 16-78)	54.5 (*SD*=24.97, 15-106)	51.1 (*SD*=21.7, 18-87)	32 (*SD=14.8, 10-61)*	24.1 (*SD=9.3, 8-35)*
10 months	*TD (n =38)*	*196.1* (306.28)	49.7 (*SD*=16.03, 25-105)	50.4 (*SD*=16.1, 14-105)	50.2 (*SD*=13.7, 27-90)	24.9 (*SD=8.4, 10-47)*	23.4 (*SD=7.6, 11-47)*
	NF1 (n= 16)	*293.73* (469.53)	73.8 (*SD*=17.7, 39-98)	73.9 (*SD*=17.16, 45-102)	73.1 (*SD*=16.2, 48-102)	35.8 (*SD=11.2, 16-50)*	37.1 (*SD=11.1, 18-56)*

Note. The number of good trials per participant was entered into a one-way (5 x 2; Condition (Standards 1,2,3; VowDev, PitDev) vs. Outcome (TD, NF1) ANOVA. The model revealed significant Age (p=.001) and Group (p=.025) effects as well as Age *x* Group (p=.009) interaction. Follow up analysis revealed higher trial numbers retained in the NF1 group. Total number of trials were therefore used as a covariate in analysis of ERP responses.

4.2.4 EEG recording and pre-processing.

Electrophysiological responses were measured using an EGI 128-electrode Hydrocel Sensor Net, with the vertex electrode used as a reference online and sampled at 500Hz (see Chapter 2.3 for details of setup and justification behind processing pipeline). A 0.01-100Hz bandpass filter was applied offline, as well as a 50Hz notch-filter to minimise the effects of line noise. The recording was then segmented into 900ms sections around the presentation of each stimulus in the auditory train (i.e. 100ms before and 800ms after stimulus presentation)[16]. Bad channels and segments were excluded through a combination of automatic artefact detection and visual inspection of individual segments (NetStation v 4.5.6.), including all epochs exceeding 150uV at any electrode. Segments with pronounced artefacts such as gross motor movement, eye blinks and/or more than 25 bad channels were rejected from analysis through hand editing. A minimum of 30% 'good' trials had to remain for the dataset to be included in the final analysis. Within the remaining segments, channels marked as having noisy data were interpolated with a clean signal from neighbouring channels using spline interpolation. As Standards 1-3 were included in each auditory train of the task, the total number of trials for these conditions is higher than the sum of trials for each deviant stimulus respectively.

For the generation of ERP waveforms, data was baseline corrected -100ms to 0ms (with 0 time = stimulus onset), re-referenced to the average of all electrodes and averaged across trials and individual datasets to generate grand average waveforms for both the TD and NF1

[16] The overlap between presentation of stimuli and segment length. For visualisation purposes, only -100 to 500 is presented.

groups. The final number of artefact-free trials differed between groups and age points for all stimulus types (See Table 4.1).

4.2.5 Statistical analyses.

In order to identify temporal regions of interest for the analysis, grand average waveforms for every participant were segmented into 50ms time bins from the onset of the stimulus (i.e. 0-50ms, 50-100ms etc.). This approach was taken rather than choosing a pre-determined component such as the P150 or the N2, due to the novelty of the paradigm and inconsistencies in the literature regarding temporal window of infant ERPs. Collapsed across group, three to four time bins with the greatest peak amplitude consecutively through visual examination, were selected for (1) Standard 1-3, given that the neural response asymptotes after a second repetition (Gruber et al., 2004; Guiraud et al., 2011); as well as (2) Standard 3 and Pitch and Vowel Deviants (Guiraud et al., 2011). For analysis of Standards, 50-200ms was identified as the temporal region of interest (time bin 2-4). Responses to vowel deviants were analysed for largest positive (50-200ms; time bin 2-4) and negative peaks (250-400; time bin 5-8, see Figure 4.5), both of which are similar temporal regions to components described in the literature[17] (Rivera-Gaxiola et al., 2005; Cheour, Leppänen, & Kraus, 2000; Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002).

Then, analysis of task effects was carried out using the identified significant time and spatial ROIs through a series of Linear Mixed Models (LMMs). Using an LMM was particularly valuable in this study, as a standard ANOVA does not include participants who do

[17] As the auditory Deviants were presented consistently at the end of each train (vs. infrequently as in classic oddball paradigm) the characteristic MMN component was not expected. Responses that may occur later in the waveform are examined, to look at possible age-dependent change in processing of native phonetic contrasts.

not have data for each time point. Independent *t*-tests or one-way ANOVAs were used for simple effects analysis following significant interactions[18]. Fronto-central ROIs correspond to regions previously used in similar tasks in the infant literature (Ethridge et al., 2016; Guiraud et al., 2011; Yagcioglu & Ungan, 2008; see Chapter 2.5.1); and demonstrated robust peaks upon visual examination of grand averaged data over the scalp regions. Greenhouse-Geisser corrections were applied where appropriate. Then, EEG metrics that revealed effects of Group and/or Age, were investigated through associations with behavioural data. These comparisons included scores on the Receptive Language and Expressive Language scales of the MSEL at 5 and 10 months of age, as well as the total of Words Understood and Words Said on the CDI at 14 months[19] respectively.

4.3 Results

EEG data was processed in NetStation (Version 4.5.6) based on the pipeline described in Chapter 2.4. Grand average waveforms were exported to produce ERP plots (Figure 4.6, 4.7). Temporal regions of interest for analysis of Standard tones was identified from peak

[18] Note that the differences in the degrees of freedom between LMMs and t-tests/ANOVAs are due to different model estimations, where LMM estimate values for missing cases and are treated in 'long format' (i.e. multiple data rows per subject; West, 2009).

[19] CDI questionnaires were sent home in a two-week time window before/after the scheduled testing date. The later time point is used for analysis as infants begin to communicate around 12 months of age, and therefore using the scale at 5-10 months would not provide an adequate range of words spoken. Previous literature has demonstrated sufficient range and reliability of this questionnaire around 14 months (Feldman et al., 2000; Fenson et al., 2000).

amplitude between 50-200ms, and for comparison of deviant tones, this was identified as 50-200ms and 250-400ms.

4.3.1 Habituation analysis (Standards 1-3; 50-200ms).

A LMM was carried out for the average amplitude over 100-200ms, with Group (TD vs. NF1), Age Point (5 vs. 10 months), Condition (Standard 1, 2, 3) and Laterality (Right vs. Left) of the Frontal ROI as fixed factors. Subsequently, Sex and total Trial number were added as covariates to the second LMM to account for within-group error variance and reduce the effect of possible confounds. The repeated covariance type was set as 'compound symmetry' and the maximum likelihood estimate was used for each model.

There was only a significant effect of Condition on ERP response (F(483)=32.21, p<.001, η_p^2=.12). Sidak corrected pairwise comparisons revealed decreased amplitude of response between Standard 1 and Standard 2 (*Mean Diff.*=2.81, *df*=483, p<.001, *CI*[1.97 3.64]), as well as a significant increase between Standard 2 and Standard 3 (*Mean Diff.*=-1.45, *df*=483, p<.001, *CI*[-2.28 -.61]). There were no significant effects of Age (F=2.98, p=.084), Group (F=.119, p=.73, η_p^2=.005) or Laterality (F=.751, p=.386, η_p^2=.01), nor significant interactions between fixed factors in the model. With Sex and Trial number added as covariates, effect of Age Point remained, which suggested that habituation occurred between the first two Standard vowels, with a preparatory response/recovery of response present in the third Standard (which always preceded a deviant). A three-way Group x Age Point x Condition interaction (F(427)=3.31, p=.037, η_p^2=.015) was also revealed. Simple effects follow-up analysis split by Group and Age Point showed that while there was a strong effect of Condition in typically developing infants at 5 (F(2,177)=17.79, p<.001, η_p^2=.23) and 10 months (F(2,231)=25.55, p<.001, η_p^2=.18), and in NF1 infants at 10 months (F(179)=17.79, p<.001, η_p^2=.12), there was no effect of Condition in the NF1 group at 5 months (F(2,93)=6.58, p=.52, η_p^2=.002). The follow-up tests suggested that there may be a lack of a habituation response in the NF1 group

at 5 months of age (see Figures 4.6 and 4.7). However, these results should be interpreted with caution as the sample size in the NF1 group at 5 months is 9, and additional Generalised Nonparametric linear mixed effects model (GLMM) analyses did not support group nor age effects, nor the three-way interaction (*p*s>.29); which is not unexpected given the reduced power offered by nonparametric tests (Mumby, 2002). Sex and Trial number alone were not significant predictors in the model (*p*s >.61).

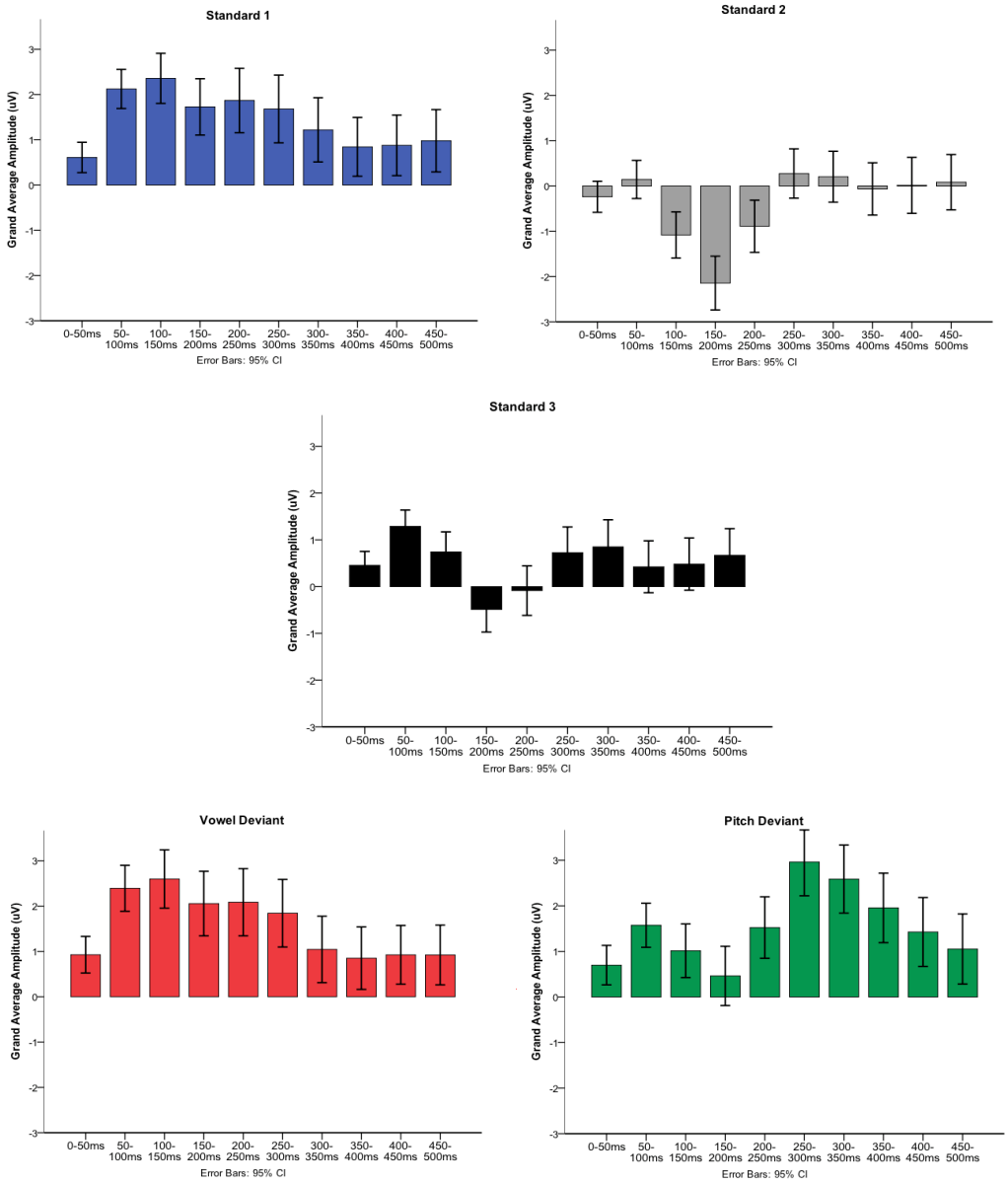

Figure 4.5 Histograms of grand average waveforms for each condition in the task collapsed across age and group, visualised across 0-50ms post stimulus onset in 50ms bins, used for identification of temporal regions of interest. For analysis of Standards 1-3, 50-200ms was selected for analysis and 50-200 and 250-400 was selected for comparison of Deviant conditions. Error bars 95% CI.

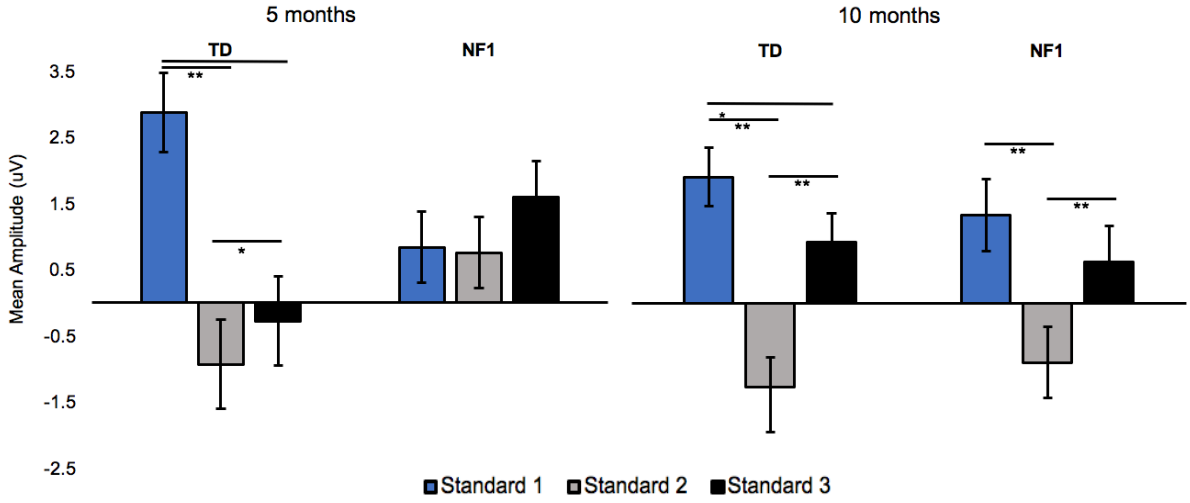

Figure 4.6 Bar plots demonstrating grand average amplitude 50-200ms following Standards 1-3 in the auditory trains task over frontal right and left ROIs. Typically developing infants showed the expected reduction in ERP amplitude following repetition, with stronger recovery of response in Standard 3 at 10 than 5 months of age. In the 5-month NF1 group, there was no evidence of a habituation response. However, at 10 months, the response was similar to the TD group, again showing recovery/preparatory response to stimulus change (i.e. onset of deviant tone). *Note.* Black lines represent condition comparisons; $**p<.001$, $*p<.05$. Error bars represent 95% CI.

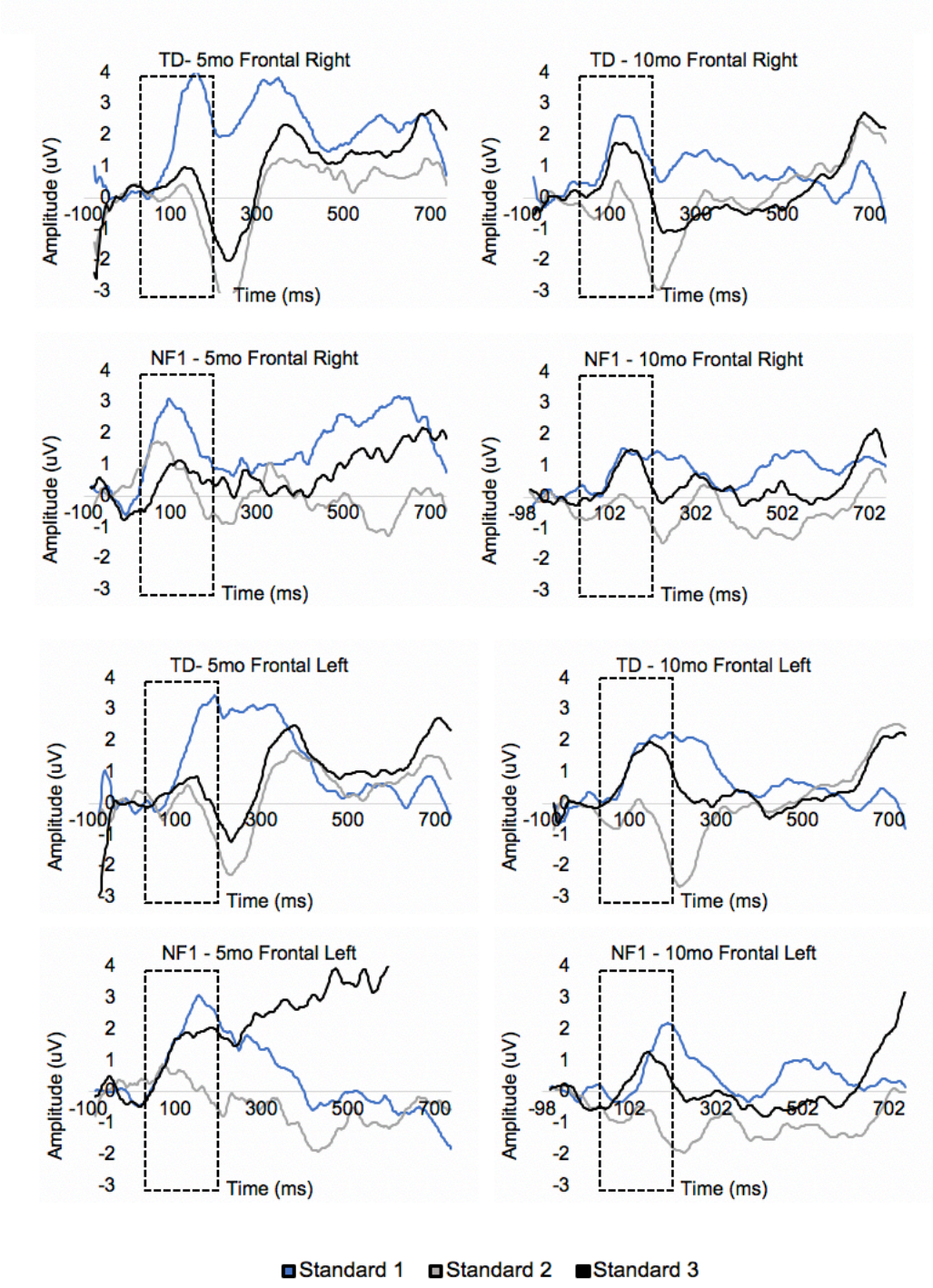

Figure 4.7 Event-Related Potential (ERP) figures from group averages at 5 and 10 months of age. Note that habituation was present between Standard 1 and Standard 2 in all groups apart from NF1 at 5 months. At 10 months of age a preparatory/ recovery response was observed at 10 months in all groups between Standard 2 and 3, which suggested that infants were able to process the pattern change with age (as Deviant tones were presented with 100% likelihood after Standard 3 on every trial). *Note.* Black dashed rectangles represent temporal ROI chosen for present analysis.

4.3.2 Change detection analysis (Standard 3 vs. Deviants; 50-200ms, 250-400ms).

Firstly, analysis of early ERP responses to auditory change (50-200ms) was conducted (see Figures 4.8, 4.9). The LMM revealed a significant effect of Condition (F(485)=11.75, p<.001, η_p^2=.046), where there was lower response amplitude for Standard 3 than Vowel Deviant (*Mean Diff.*=-1.74, *df*=485, p<.001, *CI*[-2.61 -.867]) as well as higher response amplitude for Deviant Vowel and Deviant Pitch stimuli (*Mean Diff.*=1.14, *df*=485, p=.006, *CI*[.867 2.62]). There was also a significant effect of Laterality (F(485)=4.66, p=.031, η_p^2=.009), with stronger responses in the left than the right hemisphere (*Mean Diff.*=.643, *df*=485, p=.031, *CI*[.058 1.23]). Similarly to the analysis above, there was a significant Group x Age Point x Condition interaction (F(485)=5.03, p=.007, η_p^2=.02). Follow-up analyses split by Age Point and Group revealed significant effects of Condition at 5 months in the TD group and at 10 months in the NF1 group (ps .001-.008; Figure 4.8A). However, there were no differences in responses to Deviant stimuli in the NF1 group at 5 months (p=.761, η_p^2=.0002) nor in the TD group at 10 months (p=.204, η_p^2=.0001). When accounting for effects of covariates, main effect of Laterality remained. However, neither the effect of Condition nor the three-way interaction remained significant (ps< .085), which suggested that the effect should be interpreted with caution.

In the analysis of the later portion of the ERP (250-400ms), there was a significant effect of Condition (F(490)=5.81, p=.003, η_p^2=.012). Pairwise comparisons revealed a significantly higher amplitude of response for Pitch Deviant than Standard 3 condition (*Mean Diff.*=-1.55, *df*=490, p=.003, *CI*[-2.67 -.441]). There was also a marginally significant effect of Age Point (F(490)=3.71, p=.055, η_p^2=.0013), where greater amplitude of ERP response were observed at 5 than 10 months (*Mean Diff.*=.814, *df*=534, p=.055, *CI*[-.017 1.64], Figure 4.8B). As the confidence interval crossed the zero value, it was likely that there was no meaningful difference between the age groups. No effects of Group or Laterality were observed, and there

were no interaction terms of note. With Sex and Trial number added, the effect of Condition remained (p=.007, η_p^2=.02) and effect of Age Point became non-significant (p=.641, η_p^2=.0001). Trial number but not Sex appeared as a significant covariate in the model (*Wald* Z=3.05, p=.002).

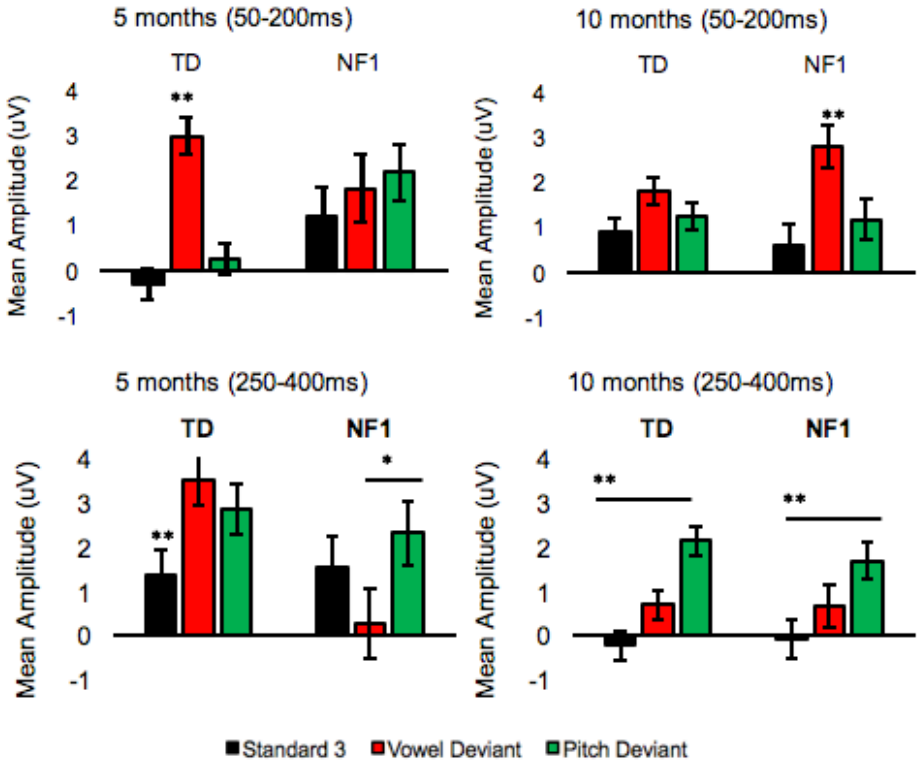

Figure 4.8 Bar plots demonstrating grand average amplitude for Standard 3, Vowel and Pitch Deviant conditions over frontal right and left ROIs averaged across **(A)** 50-200ms. TD infants showed significantly higher responses to Vowel Deviants at 5 months, and infants with NF1 showed a similar pattern at 10 months; **(B)** 250-400ms. TD infants showed the expected increase in amplitude between Standard 3 and both Vowel and Pitch Deviants at 5 months, and between Standard 3 and Pitch Deviant at 10 months. In the NF1 group, there is significantly reduced response to Vowel than Pitch Deviant (however group effects were not significant in this analysis). *Note.* Black lines represent condition comparisons, asterisks over a single bar depict the selected condition as significantly higher/lower in amplitude relative to the other two conditions; **p<.001, *p<.05. Error bars represent 95% CI.

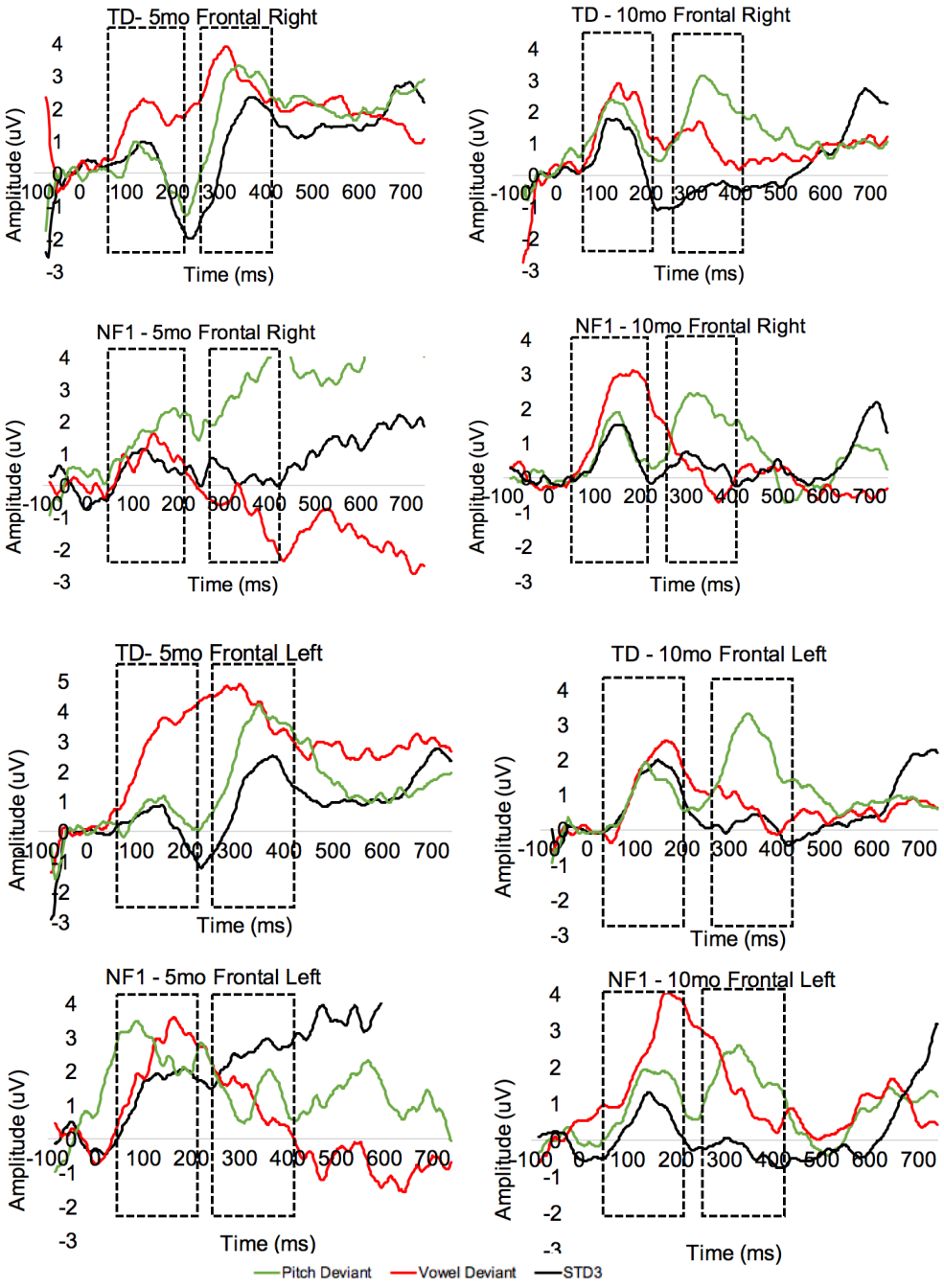

Figure 4.9 Event-Related Potential (ERP) figures from group averages at 5 and 10 months of age. Change detection was defined as significant difference between Standard 3 and Deviant Tones. While differences were observed in early change detection in the TD group (rows 1 and 3), these were present in the NF1 group at 10 months only (row 4). No group or age differences were found in the later responses (250-400ms).

4.3.3 Behavioural analysis.

Next, associations between habituation and auditory change responses and the behavioural phenotype were explored (for demographic information and average group performance on the Mullen Scale and CDI see Table 4.2). Scores on the selected scales were compared to average ERP responses to (1) Standard 2 – Standard 1 and (2) Standard 3 – Vowel Deviant for each age group. When collapsed across Age Point and Group, no significant associations with ERP amplitude were revealed. When split by Age Point, a significant negative association was found at 5 months between Habituation response and Expressive Language scores ($r(39=-.34$, $p=.034$), with higher Standards difference score (i.e. poorer habituation response) related to lower scores on the Expressive Language subscale, which is consistent with the predictions of this experiment (Figure 4.10). At 10 months, there were no associations between Standard or Vowel Deviant responses and behavioural scores, which is not surprising as no group differences were found between the NF1 and TD samples in the analysis above.

Then, ERP responses to repetition or auditory change at 5 months (as this was the time point where neural and behavioural responses differed between the two groups) were related to spoken language ability, indexed by number of words Understood/ Understood & Said (generated from the CDI parent-report questionnaire taken at 14 months of age). The model did not reveal significant associations between ERP responses and vocabulary size when split across Group or Age Point.

Table 4.2 *Group scores on observer (MSEL) and parent-report (CDI) measures of language ability for NF1 and typically-developing infants in the auditory trains task.*

	Group	Expressive Language	Receptive Language	Group	CDI-14mo Words Understood	CDI-14mo Words Understood and Said
5 months	*TD (n =22)*	47.32 (*SD*= 5.04, 35-55)	37.23 (*SD*= 12.15, 20-64)	*TD (n =23)*	123.53 (*SD*= 90.37, 21-367)	21.91 (*SD*= 22.39, 0-80)
	NF1 (n=4)	32.75 (*SD*= 8.46, 22-42)	26 (*SD*= 12, 20-44)	*NF1 (n=5)*	32.6 (*SD*= 32.04, 4-84)	2 (*SD*= 2.5, 0-6
10 months	*TD (n =25)*	36.88 (*SD*= 9.6, 26-61)	33.4 (*SD*=8.07, 20-51)	*TD (n =27)*	104.74 (*SD*= 81.9, 12-367)	26.78 (SD= 40.25, 0-167)
	NF1 (n= 13)	35.31 (*SD*= 14.54, 20-55)	35 (*SD*=8.41, 20-49)	*NF1 (n= 13)*	27.38 (*SD*= 27.31, 0-84)	3.69 (*SD*= 6.42, 0-24)

Note. Sample sizes denote all infants who attended the lab visit and completed the Mullen Scales assessment and had usable data in the ERP analysis. For scores on Mullen (5 and 10 months) and CDI (14 months of age), Standard Deviations and range of average group scores were given in brackets. Note that differences in the CDI scores at 14 months are due to different participants contributing ERP data to 5 and 10-month time points.

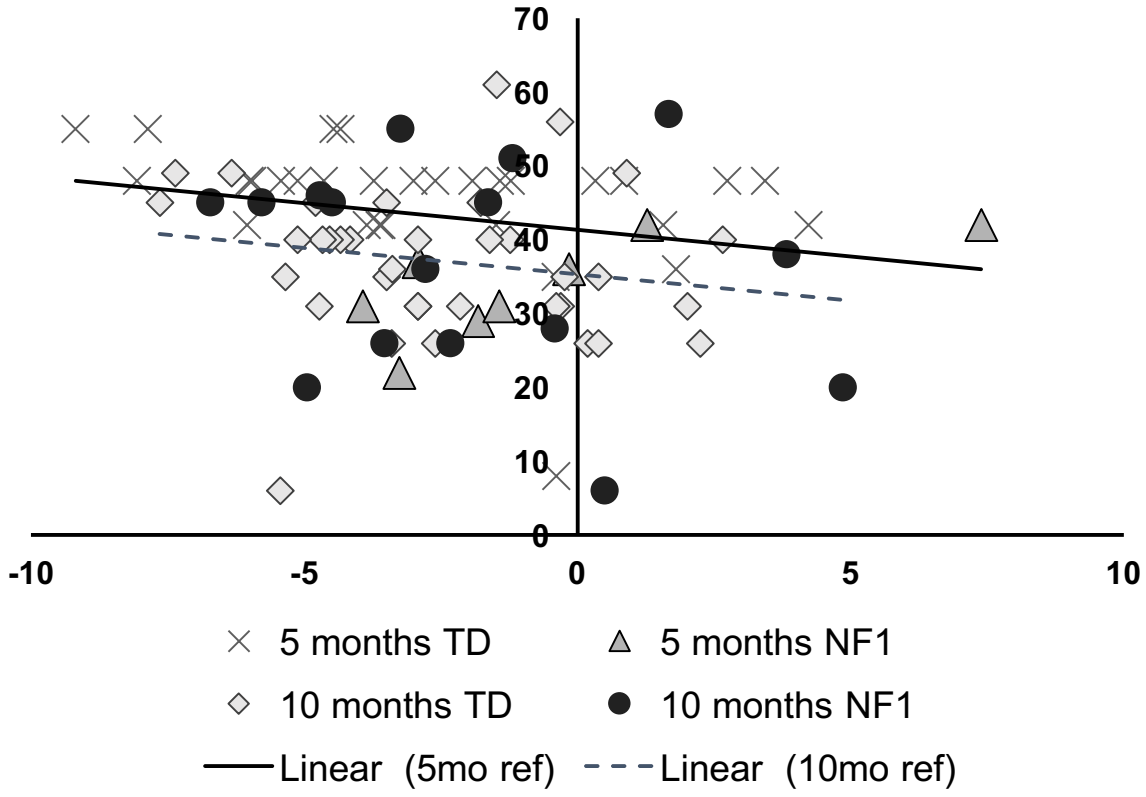

Figure 4.10 Scatterplots visualising the negative dimensional relationship between Habituation Scores and Expressive Language (partialled by Age Group). Follow up analyses revealed that the association was significant only at 5 months (irrespective of group status). No other significant associations were reported between ERP difference scores and behavioural measures of language ability in the sample.

4.4 Discussion

In the present task, I explored differences in processing of auditory repetition and change in typically developing infants, as well as infants with a diagnosis of NF1. The main hypotheses stated that there would be a strong habituation response in typically developing (TD) infants and that they will show a preparatory response to the deviant with age. On the other hand, the habituation response was expected by be reduced or absent in the NF1 group. The experiment yielded evidence for auditory habituation in the TD group through reduced ERP response over 50-200ms following repetition of the Standard stimulus, as well as evidence for recovery of response between Standard 2 and 3 by 10 months. Within the NF1 group,

however, there was no habituation response at 5 months of age, which was further related to poorer Expressive language ability in this group. In response to stimulus change, there were strong effects in response to Vowel change. No differences were observed with age, which was somewhat unexpected given the current landscape of research looking at maturational effect on infant ERPs (Cheour et al., 1998; Edgar et al., 2015; Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002). I explored the implications of these findings below and evaluated which task indices may be used as a functional index of brain specialisation.

Stimulus-specific adaptation has been previously demonstrated through a reduction in ERP amplitude following repeated tones in passive listening tasks in newborns, infants and children (Benasich & Tallal, 1996; Coch, Skendzel, & Neville, 2005; Guiraud et al., 2011; Yagcioglu & Ungan, 2008). Comparably, reduced amplitude of ERP response over 50-200ms[20] was present in the TD group at both age points. At 5 months, the habituation was protracted over 3 repetitions of the Standard in the auditory train. The group of infants with NF1 did not show a clear habituation to repetition of the Standard at 5 months, which was consistent with the original hypothesis that predicted a reduced/absent habituation response in this group. However, there was habituation at 10 months of age in the NF1 group, which suggested the possibility of age-dependent adaptation in this group.

Reduced/absent habituation has been reported in infants with atypical developmental trajectories (Ethridge et al., 2016; Guiraud et al., 2011), which is in line with present results . Possible implications of reduced habituation during very early stages of development include

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[20] The response over 150-300ms or 90-170ms has been referred to as the P150 component in the literature. However, due to the exploratory nature of the task, the temporal regions of interest were selected based on the grand average ERP responses for all participants (see Figure 4.5; Guiraud et al., 2011).

the inability to learn to ignore re-occurring, and therefore irrelevant, information from the auditory environment. Absent habituation has been studied as a possible aetiology of sensory and language difficulties in ASD (Eigsti & Fein, 2013; Rogers & Ozonoff, 2005). It was further suggested that atypical responses to repetition are the downstream effect of atypical Excitation/Inhibition balance in neuronal circuits, specifically over-reactivity to repeated stimulation (He et al., 2007). Importantly, this is the first evidence of atypical habituation response in infants with NF1, which may act as a common developmental pathway to ASD in genetic and idiopathic populations. Due to the nature of the ERP response, was difficult to disentangle the potential mechanisms involved in the processing of auditory stimuli. The association with ASD likelihood was explored further in infants with family history ASD, who also show atypical/reversed habituation responses (Guiraud et al., 2011; Chapter 6).

Additional support for auditory habituation as a useful index of brain specialisation, was the association between difference scores between Standard 1 and 2 and Expressive Language ability. The findings supported previous reports from both retrospective (Espy et al., 2004; Molfese, 2000) and prospective studies of infant development (Kuhl et al., 2006) that reported significant associations between ERP responses and behavioural phenotypes. However, no differences were observed with parent-rated outcomes of vocabulary size.

Due to the nature of the stimulus, I expected a reversal of the habituation response between the second and third iteration of the Standard stimuli, which would suggest that infants were able to predict the onset of a deviant tone (which occurred at the end of each train), which was evident at 10 months in the TD and NF1 groups. Reversal of the habituation response has been previously reported in infants using visual stimuli (Nikkel & Karrer, 1994; Pancratz & Cohen, 1970), and little evidence is currently available as to how this process may function in early infancy in the auditory domain. The findings suggested that infants show evidence of pattern learning during passive perception of vowels between 5 and 10 months of age, before

the onset of first spoken words. These conclusions warrant further investigation into this response using more complex social stimuli.

In addition, there was some evidence to support increased ERP response following Vowel than Pitch tones, although these effects disappeared when taking covariates including Trial Number and Sex into account. There were no differences in the later part of the ERP waveform, which was contrary to prediction (Cheour et al., 1998; Cheour et al., 2000; Kushnerenko et al., 2007). This could be explained by to the nature of the stimulus, whereby infants were able to encode the pattern of the auditory trains and the positive late component reflected the higher order processing. On the other hand, positive responses to speech contrasts in infants under 12 months have been reported just as frequently in change detection paradigms (i.e. mismatch negativity). Dehaene-Lamberts and colleagues (1994, 1998) showed positive ERP responses to speech contrasts in infants under 6 months. Another study reported a positivity, rather than a negativity, in response to speech contrast in the first year (Leppänen, Pihko, Eklund, & Lyytinen, 1999). These responses have been termed the 'PMMN' or 'positive MMN' components, although the mechanistic differences behind the positivity are not yet understood. A review by He and colleagues (2007) suggested that there are different maturational timetables for processing of different sounds and highlighted the variability in methodology and stimuli design for these studies, which increases the ability to interpret infant ERPs following auditory change with a high degree of confidence. There was clear detection of change between the last standard and the Vowel and/or Pitch deviant, which suggested that infants were able to detect differences in speech sounds in the absence of exogenous attention.

The differences in sample size of the NF1 than the TD cohort are likely to influence present analysis and interpretation of these results. ERP responses are fundamentally affected by sample size and the overall number of trials per individual (Luck, 2014), which is why trial numbers were controlled for in the models described above. The sample size of infants with

NF1 was largely constrained by the rarity of the disorder and the age of diagnosis (especially for *de novo* presentations of the disorder). Yet current findings have shown sufficient justification to the study of this population in the future in order to understand the associations between atypicalities in early processing of speech sounds relative to later communication difficulties.

Overall, the task revealed some important differences in early processing of speech sounds in typical development versus infants with a diagnosis of NF1. In the TD sample, I was able to show clear evidence of habituation response at both age groups, as well as change detection responses to vowel change. The task demonstrated the first evidence of reduced habituation to repetition in the NF1 group to native vowels at 5 months of age, which was subsequently associated with poorer language outcomes in a dimensional analysis across age groups. Further investigation in necessary to evaluate additional behavioural metrics of language comprehension as well as responses to non-speech based stimuli.

4.5 Exploring Associations Between Eye Tracking, Neurophysiological and Behavioural Markers of Specialisation in Typical Development

In an exploratory analysis, I examined the sensitivity of EEG indices of auditory processing to observable measures of early language ability. Previous studies reported neural markers of joint attention during simultaneous EEG and eye tracking recordings (Billeci et al., 2017; Kulke et al., 2017). In an exploratory analysis, I looked at potential associations between early ERP markers of auditory processing and behavioural indices of emerging specialisation from eye tracking tasks described in the previous chapter. Indices from eye tracking experiments reported in Chapter 3 do not appear to be strong stand-alone predictors of experience-dependent specialisation. In order to further validate neural predictors of language development, habituation responses were associated with individual performance on indices

taken from social processing tasks (See Chapter 3.14.1 for the list of variables from ET experiments entered) as well as behavioural scores on Mullen and CDI scales (Fenson et al., 2007; Mullen, 1995).

4.6 Methods

4.6.1 Participants.

For this comparison, the typically developing population was made up of the 52 infants recruited as part of the GABBLES cohort; see Chapter 3.2.1 for details). At the 5-month time point (age *M*=5mo15d, *SD*=9d), 49 infants completed the visit, 45 took part in the EEG and 45 completed the eye tracking protocol. At 10 months (age *M*=10m6d, *SD*=8d), 48 infants attended the visit, providing 46 EEG recordings and 48 infants completed the eye tracking protocol. No family history of genetic or neurodevelopmental disorders was reported.

4.6.2 Data.

The following analysis used data collected during the GABBLES study using, ET, EEG and behavioural metrics. The dependent variables selected as they have shown sensitivity to participant age or stimulus language in this sample (Chapters 3 and 4).

The ERP predictor variable was *habituation difference score* (i.e. difference in response between response to Standard 2 and Standard 1 over right and left Frontal electrodes). See Table 3.5, which described the dependent variables selected from eye tracking tasks. They included: Looking Time to native/non-native language stimuli and Pupil Dilation for English and Italian stimuli from Active Seeking (Task 1) as well as the Eye-to-mouth ratio for English and Dutch stimuli from Attentional shift (Task 3). Behavioural measures include scores on the Expressive and Receptive Language scales from the Mullen assessment at 5 and 10 months of age respectively, as well as CDI scores at 14 months of age, used as a proxy measure of language outcome. The data was entered into a series of correlational analyses using SPSS.

4.7 Results

4.7.1 Exploring relationships between eye tracking and EEG-based metrics of specialisation.

A correlation analysis was carried out between Habituation score (Standard 2 – Standard 1) and selected ET metrics (Looking Time, Pupil Dilation, Eye-to-Mouth looking ratio; all were averaged across native and non-native language to reduce number or comparisons and due to inconsistencies found in Stimulus Language comparisons; Chapter 3, Task 1). Bonferroni correction was applied post-hoc to control error rate due to multiple comparisons. A correlation analysis revealed a negative association between Habituation score and mean Pupil Diameter ($r(51)=-.289$, $p=.04$, $CI[-0.52\ -0.01]$), which suggested that greater habituation (i.e. reduced ERP response) was associated with higher Pupil Dilation when viewing infant-directed social stimuli. Further, this relationship remained significant after controlling for Age and Language Experience variables ($r(72)=-.233$, $p=.046$, $CI[-0.44\ -0.01]$). Figure 4.11 showed similar patterns between two age groups, which is strengthened at the 10-month time-point. Consistent negative relationship between Pupil Dilation and ERP Habituation score suggests this may be used as a combined measure of specialisation, as it strengthens over developmental time. It should be noted that the relationship between the two variables may be strengthened due to increased numbers of participants contributing data at the later time point.

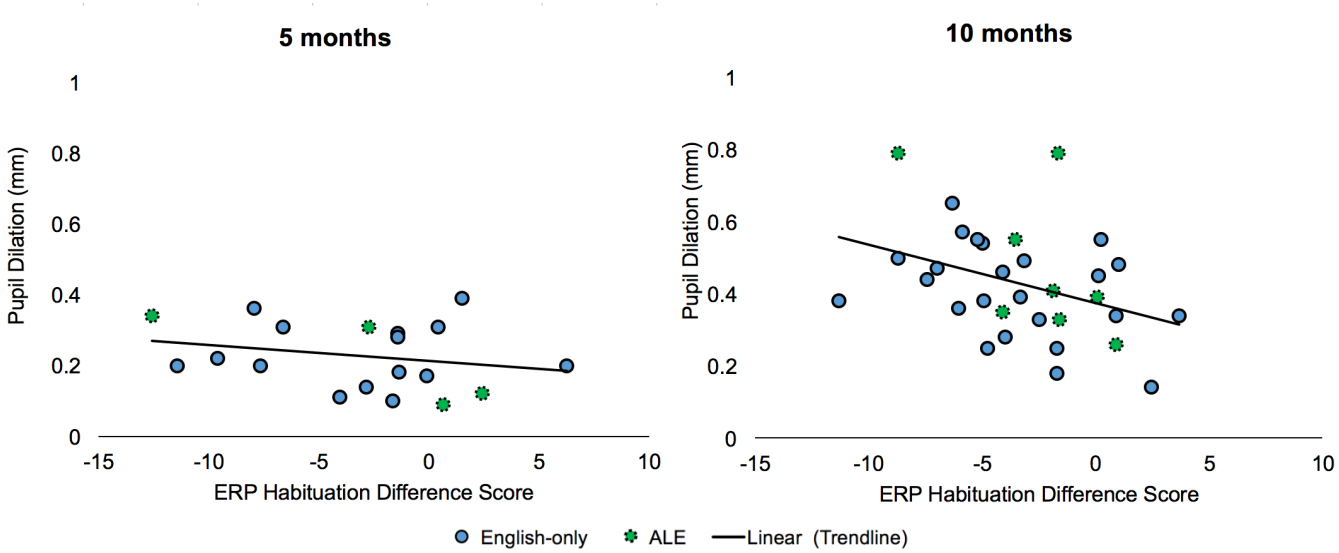

Figure 4.11 Scatterplots demonstrating significant associations between neural habituation to vowel repetition and Pupil Dilation responses in active seeking task. The plots demonstrate similar patterns between 5 and 10 months of age, with strengthened response in the older participant group.

4.7.2 Individual stability.

A *z*-score was computed for Habituation difference score and Pupil Diameter variables as a proxy *'specialisation index'* (average of two variables standardised). Higher score on the specialisation index would indicate poorer specialisation, as it would be driven by reduced differences between Standard 1 and 2. The individual scores were then correlated between 5 and 10-month time points. The analysis did not reveal a relationship between specialisation index scores between two time points ($r(42)=.113$, $p=.27$, $CI[-0.09\ 0.31]$), which suggested that the index was not internally consistent.

4.7.3 Relationship with behaviour.

Lastly, specialisation index scores were compared with behavioural metrics of language skill (Expressive and Receptive Language on the Mullen Scale, CDI Words Understood & Understood and Said). The correlation models were run for each age group separately. At 5 months, the model revealed significant associations between the provisional neuropsychological index of specialisation with Expressive Language ($r(45)=-.349$, $p=.019$,

CI[-0.58 -0.06]), Receptive Language ($r(45)=-.314$, $p=.035$, *CI*[-0.55 -0.02]) administered at 5 months and Words Understood at 14 months ($r(45)=.361$, $p=.046$, *CI*[0.36 0.59]). No significant associations with behavioural measures were observed in the 10-month age group.

4.8 Discussion

Overall, results of this exploratory analysis suggested that habituation measured through EEG may be a more sensitive marker of specialisation and may be used to supplement existing behavioural responses measured through eye tracking paradigms. Internal stability was not observed within the specialisation index (z-score for Habituation response and PD) between 5 and 10 months of age, which questioned the internal validity of the metric. It should be noted that habituation is a complex mechanism that has been regarded as fundamental to learning, and its underpinnings are still debated in the literature (Groves & Thompson, 1970; McDiarmid et al., 2019). A combined index of EEG and eye tracking measures of communication was related to several metrics of language outcome measured through observer and parent-report. Negative associations with Expressive and Receptive language appear in the predicted direction, as better habituation to repeated stimuli was related to higher language outcomes. This relationship was observed in the opposite direction for the number of words understood (CDI). This could be explained by the nature of the questionnaire, which had a large variability of scores. However, it should also be noted that the specialisation index was calculated as an arbitrary measure and was used for exploratory purposes only.

Results of this analysis suggested that electrophysiological responses may be a more accurate index of brain specialisation than eye tracking, which was examined in the previous chapter. In subsequent analyses (Chapters 5 and 6), I explored how these metrics may differ in individuals with elevated familial and monogenic likelihood of ASD. In addition to traditional ERPs, Chapters 5 and 6 further include analyses within the time-frequency domain, which have been more directly associated with regulation of E/I balance.

4.9 Chapter Discussion

Overall, results of this chapter supported the initial rationale behind investigating electrophysiological indices as a marker of brain specialisation. I was better able to detect both group and age-related changes in basic auditory processing mechanisms, relative to inconsistent results reported in a series of eye tracking experiments reported in Chapter 3. The change in methodology was therefore justified, and future chapters focused on various approaches to EEG signal processing (including power, evoked amplitude and inter-trial coherence) to detect early differences in auditory cortex function prior to onset of behavioural symptoms in infants with elevated familial likelihood of ASD or ADHD as well as infants with NF1. The following section briefly summarised and integrated the findings from the chapter above, and suggested future directions for research of typical and atypical development (see Chapter 7 for a more comprehensive overview).

4.9.1 Differences between typically developing infants and those with NF1.

One of the primary findings from this chapter was that atypical habituation to vowel repetition was observed in infants with NF1 at 5 months of age. This was further related to lower Expressive Language scores in this group (Table 4.2), which suggested that early atypicalities in speech processing may have an impact on early communicative behaviour. However, infants with NF1 did appear to 'catch up' with typically developing infants by 10 months of age in their habituation responses. On the other hand, infants with NF1 showed change detection abilty at 5 months only, with higher differences between the Standard and the Vowel Deviant. Based on the assumptions set out in the chapter above, it could be argued that infants with NF1 do not detect change between the third repetition of the Standard and the Vowel change, and only respond when the Pitch of the stimulus is altered. This is consistent with previous investigations of individuals with ASD (Bonnel et al., 2003).

One possible explanation for the overall results from the 5 month NF1 group is that in the first 6 months of life, infants acquire the basic building blocks of language, and dysregulation within this process is likely to have downstream effects on the behavioural phenotype, even if the electrophysiological responses appear to 'normalise'. Subsequently, these differences can be justified by the smaller group of infants with NF1 included in this preliminary investigation, and results must be interpreted with caution. Next, it was evaluated whether it was possible to detect a similar relationship in infants with later idiopathic ASD (Chapter 5) or elevated familial likelihood of developmental disorders (Chapter 6).

4.9.2 Habituation as a translational marker of specialisation.

Another important finding was that the EEG indices of habituation were sensitive to age and showed significant associations with early communication abilities. Habituation is a fundamental brain mechanism, which has been consistently reported in participants of different ages as well as showing robust age-dependent changes in cross-sectional cohorts (Cohen, Gelber, & Lazar, 1971; Ethridge et al., 2016; Guiraud et al., 2011) as well as animal models (Lovelace et al., 2016; Olexová et al., 2013; Sinclair, Featherstone, et al., 2017). The exploratory analysis presented in this chapter showed that, for the first time in a longitudinal developmental study, there were significant associations between EEG, eye tracking and behavioural measures. In order to fully explore the stability of these measures as a combined index of specialisation, larger sample sizes are required. Additionally, repeated individual testing would be required in order to establish test-retest reliability. It should be noted that the EEG task itself was simplified relative to the traditional habituation paradigms (such as the one used in Chapter 5), and therefore may not be directly comparable to the current literature.

4.9.3 Future directions.

Results of the auditory trains task showed sensitivity to age and group status, which is explored in the forthcoming chapters of this work. Specifically, I investigated whether similar

patterns of responses are observed in idiopathic ASD; and whether the direction of effects is similar between neurophysiological responses and behavioural phenotype across developmental or genetic conditions. Instead of focusing on age-dependent effects as the main dependent variable, as discussed above, I focused on exploring individual predictors of typical vs. atypical development in order to identify effective therapeutic targets. In order to achieve this, more traditional experimental paradigms were adapted (such as auditory oddball and frequency modulation designs) across several distinct infant populations. This was done in order to expand upon current knowledge of the relationship between basic auditory processing and emergence of communicative ability, as well as connect predictions made from animal models in a non-invasive way during early stages of development.

In the following two chapters of the thesis, I explored how neural specialisation of auditory perceptual mechanisms may differ in infants with elevated likelihood of Autism Spectrum Disorder due to elevated familial or genetic load (i.e. infants with a diagnosis of Neurofibromatosis Type 1). The EEG tasks described below looked further into neural mechanism function at specific age points where auditory specialisation has been assumed to take place in neurotypical infants. Any atypicalities within these sensory responses can suggest early processing difficulties, which can be utilised as biomarkers or potential treatment targets. This was achieved by decomposing EEG signal into its constituent frequencies, i.e. time-frequency analysis of an auditory mismatch negativity task (Chapter 5) and auditory steady-state responses (Chapter 6).

Chapter 5. Auditory Responses to Repetition and Change in Infants with Familial Likelihood of ASD

This chapter investigated the underlying mechanisms of atypical auditory processing in infants with elevated familial likelihood of ASD. Sensory sensitivity is a symptom experienced by up to 90% of individuals with ASD and has been described as both hyper- and hypo-responsiveness (Dickinson, Jones, & Milne, 2016; Guiraud et al., 2011; Jones, Dawson, & Webb, 2018; Linke, Jao Keehn, Pueschel, Fishman, & Müller, 2018; Matsuzaki et al., 2014), and is rated as the most pervasive symptom of the disorder (Billstedt et al., 2007; Leekam et al., 2007). In contrast to other empirical chapters featured in this thesis, the chapters below feature analyses from one age group with varying degrees of familial (Chapter 5 and 6) or monogenic likelihood of ASD (Chapter 6). Evidence presented in this work is among the first studies to show dysregulation in cortical processing in early infancy as a potential mechanism of altered experience-dependent specialisation in the developing brain, preceding the onset of the behavioural phenotype associated with ASD. Specifically, the analysis looked at different

aspects of electrophysiological activity during an auditory oddball task in an infant sibling population (see Chapter 1.5.2 for definition). Atypicalities in the expected habituation or change detection responses have been widely reported in literature on early development and processing in children and adults with ASD (Kemner, Oranje, Verbaten, & van Engeland, 2002; Matsuzaki et al., 2014; Takarae & Sweeney, 2017; Wang et al., 2013).

Data collection was completed as part of the British Autism Study of Infant Siblings (BASIS – Phase II; http://www.basisnetwork.org) in 2014-15 by the researcher team at CBCD, Birkbeck College. My contribution was pre-processing and analysis of demographic, behavioural and electrophysiological data. Analysis and interpretation of the data featured in this chapter is considerably altered due to differences in the nature of the research questions and advanced in analytic practices. A portion of the data appeared in article: Kolesnik, A. et al., '*Increased cortical reactivity to repeated tones at 8 months in infants with later ASD*' with substantial modifications (see Originality Statement).

5.1 EEG Task 2: Cortical Responses to Repetition and Change in 8-Month-Old Infants with Later ASD

Irrespective of the wealth of research into manifestations of ASD, there is still relatively little understanding of early contributors to atypical development of social communication and generalised processing difficulties. Moreover, several studies have reported these to be the most debilitating aspect of the disorder (Billstedt et al., 2007; Leekam et al., 2007). Note that the auditory oddball task described in this chapter explored habituation and change detection responses that are different from Task 4. For this task, I focused on replicating established paradigms in order to examine their sensitivity to detecting early differences predictive of developmental outcome. The auditory oddball task has been described extensively in the

literature, which increases the ability to characterise any potential underlying mechanisms of atypical function.

One of the most influential theories of ASD has implicated dysregulated coordination of excitatory and inhibitory (E/I) balance in cortical processing and associated homeostatic/autoregulatory feedback loops (Johnson, Jones, & Gliga, 2015; Lee, Lee, & Kim, 2017; Nelson & Valakh, 2015; Rubenstein & Merzenich, 2003; Rubenstein, 2010; Selten, van Bokhoven, & Nadif Kasri, 2018; see Chapter 1.6.1 for review). The high co-occurrence of epilepsy in individuals with ASD supports this hypothesis (incidence estimates around 22%; Bolton et al., 2011), in addition to the high rates of ASD in genetic disorders that disturb GABA-ergic functioning, the primary source of inhibitory signalling in the brain, including Fragile X, 15q11-13 and Neurofibromatosis Type 1 (Coghlan et al., 2012; D'Hulst et al., 2006; Isshiki et al., 2014).

5.1.1 Excitation/inhibition imbalance in ASD[21].

There has been a considerable amount of evidence that has linked dysregulation in the E/I balance to ASD, but in order to identify a relationship to the behavioural phenotype – disruptions in cortical processing have to be identified prior to onset of symptoms. Genetic studies reported that risk factors for alterations within the E/I signalling pathway appear prenatally, including mutations in genes later involved in synaptic development and function (Lee et al., 2016; Lionel et al., 2013; Selten et al., 2018). Yet, there is limited understanding as to the full implications of E/I for brain maturation, which can be attributed to the dynamic shifts of neurotransmitter activity in early development (Dorrn et al., 2010; Sun et al., 2010). The

[21] Also see *Chapter 1.1.1*, which outlined the functional changes and emergence of excitation/inhibition balance in typical development.

importance of the interplay between E/I signalling has been further supported by the finding that excitatory activity in the Nrg1/ErbB4 signalling pathways[22] control development of inhibitory circuitry in the mammal cerebral cortex by regulating connectivity of GABA-ergic neurons (Fazzari et al., 2010). Animal studies have shown that dysregulation in development and subsequent function of these candidate interneurons may alter plasticity and present as a common pathway underlying neurodevelopmental disorders including schizophrenia and ASD (Hahn et al., 2006; Marín, 2012). Additionally, evidence from individuals identified with SCN2A[23] mutations has shown that over-excitation in the first year of life, but not later on in development, was associated with later ASD diagnosis (Ben-Shalom et al., 2017; Sanders et al., 2012; L. A. Weiss et al., 2003).

The literature has further emphasised the importance of first year of life as a window to observe these alterations, which is essential in order to provide effective pre-emptive interventions (Webb et al., 2013; Yizhar et al., 2011). Several pharmacological manipulations which affect the E/I pathway are currently available (Bethea & Sikich, 2007; Calfa et al., 2015; Olmos-Serrano et al., 2010; Spooren et al., 2012), however there is no target cortical 'outcome'

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[22] Neuregulin 1 (NRG1) is a protein molecule encoded by the NRG1 gene, found to affect GABAergic neurotransmitter systems (Woo et al., 2007). ErbB4 is a tyrosine kinase receptor of NRG1, and their combined activity affects glutamatergic and GABAergic transmission and has neurotrophic effects. Phenotypic expressions of dysregulation in this pathway include locomotor difficulties, cognitive and social communication impairments (Banerjee et. al., 2010).

[23] SCN2A is a gene which encodes sodium channel Nav1.2, responsible for development of mature neurons including glutamatergic pyramidal cells. It was one of the first genes ASD-associated genes and remains one of the strongest candidates (Sanders et al., 2015).

measure that is used to index improved function in humans. One way of finding an outcome measure in a non-invasive way with infants is to identify putative EEG-based indices.

5.1.2 Habituation, E/I and ASD.

One way to study cortical excitability as an outcome of dysregulated E/I is to look at differences in basic sensory processing. Problems in any system are more likely to arise if the it is repeatedly stimulated. As described in Chapter 4.1.1, habituation is a dampening of response following repetition of a stimulus. It requires the system to differentiate between 'old' and 'new' stimuli. The inability to make those codes results in an absence of an attenuation of a neural response, i.e. stimuli are not recognised as old, means that the system receives the same amount of input with each repetition. This may in turn overload sensory processing systems and lead to development of a hyper-responsive perceptual system in its mature state. This is supported by evidence of atypical responses to repetition in Fragile X (Ethridge et al., 2016; Knoth et al., 2018), which is a genetic disorder with increased incidence of ASD relative to the general population (20% for females and >50% for males; (Kaufmann et al., 2017)) where evidence of increased cortical excitability is also present.

As well as evidence of atypical habituation responses in infants and child populations with elevated familial likelihood of ASD (Guiraud et al., 2011; Levin et al., 2017; Righi, Tierney, Tager-Flusberg, & Nelson, 2014; Snijders, Milivojevic, & Kemner, 2013; Snyder & Keil, 2008); neural responses to repetition have further been linked to neurotransmitter activity regulating inhibitory control (Auksztulewicz & Friston, 2016; Lawson et al., 2014; Takarae & Sweeney, 2017). For example, it was found that blocking GABA activity in the inferior colliculus showed higher neural responses to repeated stimuli and activating GABAergic receptors in the medial geniculate body reduced responses to repetition (Duque et al., 2014). Prospective studies in infant populations are necessary to understand the association between

early atypicalities in auditory habituation response and the behavioural phenotype in a non-invasive way, which has the potential to inform effective interventions.

5.1.3 Mismatch negativity and atypical change detection in ASD.

Another way of examining functional specialisation of the auditory cortex is by looking at cortical responses to change. In ERP literature, change detection is characterised by the Mismatch Negativity (MMN) response, which is a negative peak occurring between 100-300ms (He, Hotson, & Trainor, 2007; Näätänen, Paavilainen, Rinne, & Alho, 2007) as well as the P3a, a positive going peak detected between 200-400ms post stimulus onset (He et al., 2007; Soltani & Knight, 2000) believed to represent automatic change detection and orienting responses. As highlighted in Chapter 4.1.2, tone repetition forms a representation in a neurotypical system, which is violated by an auditory oddball. Failure to construct a representation of the repeated stimulus, means that change detection response is less distinguished. The argument has been supported by many studies that showed a reduced/absent change detection response in children and adults with ASD (Dunn, Gomes, & Gravel, 2008; Sinclair, Oranje, Razak, Siegel, & Schmid, 2017; Vlaskamp et al., 2017). This was further associated with language difficulties, as failing to discriminate speech sounds early on was thought to affect the infant's ability to decode and produce sounds themselves (Eigsti & Fein, 2013; Roberts et al., 2011). Indeed, there have been suggestions of using the MMN paradigm in clinical settings to detect atypical function of the auditory system in neurodevelopmental disorders (Näätänen, Sussman, Salisbury, & Shafer, 2014; Schall, 2016), which suggested that it may be a useful assessment tool for auditory processing in infancy. There is need to evaluate time-frequency responses to auditory change, as it may provide further information about the potential neural mechanisms involved in these responses.

However, there may be difficulties in interpreting neurophysiological responses in infant populations, due to large individual variability as well as age-related changes in ERP

responses that occur in the first years of life (Kushnerenko et al., 2002a; Kushnerenko et al., 2002b). Additionally, there are inconsistencies in developmental trajectories responses to pitch deviants in infant MMN studies (Cheour-Luhtanen et al., 1995; Ghislaine Dehaene-Lambertz & Baillet, 1998; Trainor et al., 2001), which may be due to task design and statistical analyses used (He et al., 2007). These will be further addressed in the Discussion section of this chapter.

Taken together, examining neural responses to Habituation and Change Detection in early infancy may provide a valuable index of cortical reactivity that is sensitive to alterations in coordination of E/I activity.

5.1.4 Present study.

The task presented in this chapter was used to examine neural responses to an oddball paradigm conducted with 8-month-old infants at low (*n*=27) and high (*n*=116) familial likelihood of ASD. Infants with family history of ASD have a 20% chance of receiving a diagnosis in childhood (Ozonoff et al., 2011), and thus prospective studies of this population are essential to allow examination of causal paths to the disorder (see Chapter 1.5.2). Previous reports of ERP data (which included a portion of the sample described below) reported a reduced habituation response to pure tones in infants with family history of ASD relative to infants with no family history of neurodevelopmental conditions (Guiraud et al., 2011). It should be noted that no outcome data was available at the time, and the majority of the sample were typically developing. In the present study, I examined both the ERP response to pure tone stimuli and the underlying spectral activity in a larger sample of the same study, by breaking the signal down into different frequency bands (Cohen, 2014; Varela, Lachaux, Rodriguez, & Martinerie, 2001) and looking retrospectively at the effect of developmental outcome.

Due to concern of multiple comparisons and the likelihood that differences in gamma-band responses may be subtle, two *a priori* analytic decisions were made prior to statistical analysis of the data. Temporal windows, AOIs and frequency bands were selected based on

responses observed in the typically developing group. Specifically, preliminary analyses were carried out to identify bands/areas associated with reduction of amplitude of gamma responses across repeated and novel notes in the Typical Likelihood (TL) group. The analysis of the elevated-likelihood of ASD group was then restricted to bands/areas of interest within each analysis (habituation vs. response to change). The chosen analysis strategy reduced the effect of multiple comparisons within the Elevated Likelihood (EL) group analysis, but did increase the possibility that there are differences in other scalp regions. Note that for the ITC analysis, comparable ROIs were used, while the temporal window of interest was determined by previous literature (Ethridge et al., 2016) and examination of the grand averaged response due to the limited number of studies of ITC in infants.

Secondly, group differences between infant sibling groups. One possible approach to this analysis is to compare primary indices of interest across all 'outcome' groups (Christensen et al., 2010; Wan et al., 2013), which in the present sample would include infants with typical likelihood[24] (TL), elevated likelihood with later typical development (EL-TD), elevated likelihood with atypical development (EL-Atyp) and infants with elevated likelihood with later ASD (EL-ASD). This path was not used, however, as the TL group was used to identify windows of interest, and including them in the group comparison would skew the findings. The intermediate group, EL-Atyp, was also excluded from the main analysis as (1) including the group would reduce power and (2) no clear predictions could be made about this group due to high variability of symptoms rated as 'atypical'. However, the EL-Atyp group was included in exploratory follow-up analyses which were reported in Appendix H. The strategy that was

[24] Infants with no family history of developmental disorders; population prevalence studies reveal that 1.1-3% have ASD (Baron-Cohen et al., 2009; Brugha et al., 2012; Williams, Higgins, & Brayne, 2006).

chosen for this analysis compared responses between EL infants with later typical development and those with later ASD, which closely resembled the case/control approach previously used in the literature (Jones & Klin, 2013; Ozonoff et al., 2010; see 5.2.6 Analysis Strategy for details).

In response to repetition of the 'Standard' frequency stimulus it was expected that there would be a suppression/reduction in activity with stimulus repetition in the TL infants (i.e. habituation response), specifically a reduction in P150 ERP component, as well as reduced gamma amplitude and 10-20Hz ITC (Ethridge et al., 2016; Yu et al., 2018). For frequency deviant stimuli, greater amplitude of the negative going component MMN was expected versus the sum of standard tones in the TL group.

As the ERP-based indices of habituation have been reported as atypical in ASD in previous work (Guiraud et al., 2011; Roberts et al., 2011) and linked to E/I imbalance (Ethridge et al., 2016; Matsuzaki et al., 2014; Snijders et al., 2013), an absence or a reduction in P150 response with stimulus repetition was expected in EL-ASD relative to the EL-TD group. Further, a reduced habituation response was expected within the gamma band activation, as well as elevated phase-coherence to repeated tones in the EL-ASD group. Based on findings of atypical responses to auditory change detection in ASD, reduced amplitude of gamma activity was expected following deviant stimuli in EL-ASD vs. EL-TD groups (Benasich & Tallal, 2002; Gomot et al., 2006; Roberts et al., 2011), as well as a reduced amplitude of both MMN and P3a ERP components. Note that due to the smaller number of trials for deviant stimuli prevalent to oddball paradigms, ITC was not examined for these conditions.

A further exploratory analysis was carried out to examine the full dimensional nature of the EL design was exploited by examining associations between a composite score of gamma activation and ITC responses to Standard tones only, later termed the Cortical Reactivity Index, and variation in later language skills across the whole cohort (TL, EL-TD,

EL-Atyp, EL-ASD; Edgar et al., 2013; Seery, Tager-Flusberg, & Nelson, 2014). The term 'reactivity index' was selected to represent the conceptual nature of spectral EEG responses. Specifically, when a repeated train of stimuli are encountered ongoing oscillatory activity in the brain can change in two ways; (1) the power or amplitude of oscillations can increase in response to the stimulus and/or (2) the phase of the oscillation can align with the timing of the stimulus in a consistent way across trials (Makeig et al., 2004). Both these reactions produce larger amplitude event-related brain responses and thus, in a conceptual sense, reflect increased reactivity. Thus, reduced gamma habituation and higher ITC would additively work to produce a higher cortical reactivity index.

Previous studies have reported strong associations between early auditory processing and language development, suggesting that early learning (habituation and change detection) of simple stimuli play an essential role in acquisition of more complex speech sounds (Benasich et al., 2002; Benasich & Tallal, 2002). Further, failure in these basic learning mechanisms may indicate alterations in neural organisation, consistent with observations of atypical neural connectivity in developmental disorders, as well as differences in the coordination of excitation and inhibition (Delbruck et al., 2019; Ethridge et al., 2016; Linke et al., 2018; Rubenstein & Merzenich, 2003). It was expected that higher scores on the index would be positively associated with parent-report measures of ASD-related symptomology at 3 years (SRS-2; Constantino, 2012). It was further expected that significant differences in deviance detection responses would show dynamic associations with behavioural measures of ASD symptomology.

5.2 Methods

5.2.1 Participants.

Participants were 116 (64 male; 52 female) infants with elevated likelihood (EL) and 27 (14 male; 13 female) infants with typical likelihood (TL) of ASD. All infants in the EL group had an older full sibling with a community clinical diagnosis of ASD (recruited from the British Autism Study of Infant Siblings running between BASIS; http://www.basisnetwork.org). Infants in the TL group had no reported family history of ASD or any other developmental or genetic disorders (recruited from a volunteer database at Birkbeck Centre for Brain and Cognitive Development), and had at least one older full sibling. Infants recruited for the study attended four visits, at 8 months and 14 months, with follow up visits at 2 and 3 years. EEG data for the present study is taken from infants during their 8-month visit (*M*=9mo3d, *SD*=30d) and outcome data from the 3-year visit (*M*=39mo1d, *SD*=3mo2d). The study was approved by the National Research Ethics Service London Central Ethical Committee (08/H0718/76) and conducted in accordance with the Declaration of Helsinki (1964). Further details of inclusion/exclusion criteria and proband diagnostic phenotyping refer to Clinical Assessment in Appendix H.

Within the EL group, developmental outcome at 3 years was used retrospectively as a grouping variable. Sixty-four infants were considered typically developing and constituted the EL-TD group. Seventeen infant siblings met gold-standard criteria for ASD (determined by consensus clinical judgment of a group of expert clinical researchers based on information including the ADOS-2, ADI-R and interaction with the child; See Appendix I) and constituted the EL-ASD group. Lastly, 32 infant siblings were classified as atypically developing, i.e. displayed some developmental concerns but did not meet criteria for an ASD diagnosis (EL-Atyp). Following data cleaning procedures (see Chapter 5.2.4 and Chapter 2.4), 131 participants provided sufficient EEG data for analysis (N_{total}= 94/113; *TL*=14/27; *EL*-

TD=45/64; *EL-Atyp*=21/32; *EL-ASD*=14/17; see Table 5.1). Sensitivity analysis (Faul et al., 2009) of the total sample size with a power of 1-β = .80 revealed a population effect size of *d*=.21.

5.2.2 Stimuli and apparatus.

Sounds were presented in an oddball paradigm originally designed by Guiraud and colleagues (2011). Duration of each sound stimulus was 100ms, with 5ms rise and fall time. The inter-trial interval was 700ms. A 'Standard' pure tone at 500Hz was presented with an 77% probability. The paradigm also included two deviant or infrequent tones, which were presented with a 11.5% probability each. One infrequent sound was a pure tone of 650Hz, termed the Pitch Deviant as well as a White Noise deviant that was matched for temporal duration. The sound intensity was 70dB SPL. The sounds were presented for 5-7 minutes or until the infant became too restless, which on average yielded 477 trials for TL and 462 trials for EL infants (See Table 5.1 for trial breakdown per participant group and condition). Following Guiraud and colleagues (2011) and *a priori* hypotheses, responses to the first, second, and third presentation of a Standard tone were examined as well as responses to the Pitch Deviant and White Noise stimuli versus the sum of all Standard tones (i.e. Standards 1-19).

5.2.3 Procedure.

The auditory oddball task was administered at the end of a battery of visual EEG tasks. Infants were seated on the parent's lap facing the experimenter, who blew soap bubbles throughout the recording session to keep the infant calm and engaged. The experiment was conducted in a sound attenuated room, where the sounds were presented from two speakers, 1 metre apart, and located 1 metre in front of the infant. The Mullen Scales of Early Learning (Mullen, 1995) were administered in the standardised format; with assessments completed in the same laboratory setting by a small team of experimenters. Parents were also asked to

complete a set of questionnaires at home within two weeks of each laboratory visit, including the Social Responsiveness Scale (Constantino, 2012) at 3 years of age.

5.2.4 EEG recording and pre-processing.

Electrophysiological activity was measured as described in Chapter 4.2.4. The recording was segmented into 1000ms sections (500ms pre- and 500ms post-stimulus presentation). Bad channels in each segment were marked by automatic artefact detection and visual inspection in NetStation (v 4.5.6). All epochs exceeding 150μV at any electrode were excluded through automatic artefact detection. The segments with pronounced artefacts, i.e. gross motor movement, eye blinks, or more than 25 bad channels, were rejected from analysis through hand editing (104 clean datasets remained). At least 30% of trials had to be retained in each category to qualify the dataset to be included in the group analysis. For the remaining trials, channels with a noisy signal were interpolated from neighbouring channels with a clean signal using spline interpolation. Following Guiraud and colleagues (2011) and Seery and colleagues (2014), all standards that followed either Deviant were categorized by position and only the first three were selected for habituation analysis (Standard 1, Standard 2, and Standard 3). There was only one restriction during stimulus presentation – that the deviant sound had to follow at least two standard tones. Due to this, there were notably fewer Standard 3 trials administered relative to Standard 1 and 2. The final number of remaining, artefact free, trials did not significantly differ between groups for the three stimulus types (all *p*s>.05, see Table 5.1). For analysis of ERP waveforms, data was then baseline corrected -100ms to 0ms prior onset of stimulus, re-referenced to the average of all the electrodes and averaged together over trials and group status to form grand average waveforms.

5.2.5 Wavelet transform.

For time-frequency analysis of the signal, hundred and four pre-processed datasets (following bad channel replacement) were exported into MatLab® using the free toolbox

EEGLAB (Version13.6.5b, http://sccn.ucsd.edu/eeglab/) and re-referenced to the average reference. For analysis of evoked gamma, epochs of raw EEG data were averaged together. A custom-made collection of scripts, WTools, (available upon request from Dr Eugenio Parise[25]) was used to compute complex Morlet wavelets at 1Hz intervals between 1 and 80Hz. A continuous transformation was applied to all epochs through convolution with a wavelet at each frequency in the chosen range, taking the absolute value as a result (i.e. amplitude not power[26], (Parise & Csibra, 2013)). To reduce distortion created by convolution, padding of 100ms at the start and end of the segment was applied to the individual datasets. A baseline period was set between -200 and 0ms and subtracted from the post-stimulus responses to remove any residual 50Hz (electrical) noise in the data[27] and to control for pre-stimulus preparatory activity. Four regions of interest (ROIs) in the left and right frontal and tempo-parietal cortex were chosen based on previous investigations into auditory gamma activity (Guiraud et al., 2011; Kushnerenko, Ceponiene, Balan, Fellman, & Naatanen, 2002; Figure 2.4). Amplitude was extracted for low (20-40Hz) and high (40-60Hz) gamma bands (30-150ms post stimulus onset). The low and high bands were derived from previous examinations of gamma band activity in infants and children (Grossmann et al., 2007; Rojas et al., 2008). Such evoked (rather than induced or baseline) gamma reflects responses time-locked to the stimulus, reducing the likelihood of contamination by muscle artefact or electrical noise. Next, inter-trial

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[25] Available from Dr Parise via email: eugenioparise@tiscali.it.

[26] Note that data in Chapter 6 was processed through a different pipeline using absolute power within a frequency band (equal to amplitude squared).

[27] No 50Hz filter was used in this analysis as 50Hz was included in the average of the frequency bands of interest (unlike Chapters 4 and 6, where a notch filter was applied).

coherence (ITC) measures were calculated (collapsed across all standards to improve signal-to-noise ratio). This measure represents whether the distribution of phase angles in a single time-frequency point are uniform, with 1= perfect phase consistency across trials and 0 = completely random phase angles (Cohen, 2014; Tallon-Baudry & Bertrand, 1999; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). When extracting ITC, small trial numbers can artificially skew results (Cohen, 2014). To identify whether a phase-locking response occurred, Standard tones 1-3 were used such that there were at least 100 good trials included per infant. Individual number of trials per dataset were entered as covariates in the model, which also reduced the possibility of introducing further biases from selecting a fixed subset of trials. This represents a relatively stable ITC response relative to previous literature, where the common cut-off for the number of trials used ranges from one (Milne, 2011) to between 200 and 800 (Musacchia et al., 2015; Nash-Kille & Sharma, 2014), with many studies not reporting the total number of trails used for analysis (Bosseler et al., 2013; Ortiz-Mantilla et al., 2016). Average ITC was extracted using EEGLAB functions in the 10-20Hz band, with this frequency band and temporal windows selected based on the aggregated grand average, previous work with individuals with Fragile X (Ethridge et al., 2016) and the onset timing of the P150 infant ERP component, which has been shown to be sensitive to reduced habituation in a subset of the EL infants (100-180ms; Guiraud et al., 2011).

5.2.6 Analysis strategy.

The analysis approach was designed to constrain the number of contrasts made in testing effects of developmental outcome (i.e. to minimise Type 1 error and maximize power in this relatively modest sample). Accordingly, gamma responses to tone repetition were first analysed within the TL group from which the topography, temporal region and frequency band of interest were identified. Habituation was defined as a reduction in gamma amplitude between the 1st and 3rd standards, given that oscillatory response asymptotes after a second

repetition (Gruber et al., 2004)[28]. Change Detection (CD) was defined as a significantly higher/lower ERP/gamma amplitude between the sum of Standard tones (Standards 1-3) and Frequency Deviant or the White Noise Deviant. Analysis was then restricted to the significant spatial and temporal ROI and frequency band, and contrasts were performed between EL-TD and EL-ASD groups (Mitchell et al., 2006; Ozonoff et al., 2010). Greenhouse-Geisser corrections were applied where appropriate. Similarly, differences in phase-locking values were identified by comparing ITC in the significant ROIs over the scalp region used in analysis for EL-ASD and EL-TD groups for the average of all Standard tones. The EL-Atyp group were excluded from the main chapter to maximise power. Yet, data from the EL-Atyp group was processed in additional analyses and is reported in Appendix H.

Next, significant auditory responses to Standard tones (i.e. evoked gamma and low-frequency ITC) were used to create a 'Cortical Reactivity Index' (CRI) by *z*-scoring values of the chosen index measure across the cohort (reduced habituation of gamma amplitude and greater ITC would give a higher CRI score), and then averaging the values for each individual.

Lastly, a dimensional behavioural analysis was carried out on the CRI scores. Behavioural measures included development in language skills (difference scores of Expressive and Receptive Language subscales, calculated by subtracting 8-mo from 36-mo scores) (Mullen, 1995), ADOS severity scores (ADOS-2 Gotham, Pickles, & Lord, 2009) at 36 months, as well as the *t*-score of the score on the Social Responsiveness Scale™ (SRS™, Constantino, 2012) reported at 36 months.

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[28] Unlike the Auditory Trains task described in Chapter 4, the number of standards presented in a row was randomised and therefore no prediction responses could be detected.

Table 5.1 *Sample size and descriptive statistics (mean, standard deviation and range) of trials retained for all participants included in the analysis of the auditory oddball task. Total trials depict the number of trials administered.*

Group	Total Trials	Standard (Pure tone at 500Hz)				Pitch Deviant (Pure Tone at 650 Hz)	White Noise Deviant
		Total	*STD1*	*STD2*	*STD3*	*D1*	*D2*
TL (n =14)	467	177 (SD = 54.6, 106-261)	48 (SD=16.29, 24-75)	48 (SD=17.9, 21-74)	28.9 (SD=11.6, 12-50)	29.1 (SD=8.08, 20-44)	30.3 (SD=6.99, 20-43)
EL-TD (n= 45)	468	188.6 (SD= 58.04, 108=361)	50.2 (SD=16.2, 29-91)	57 (SD=15.4, 31-93)	34 (SD=10.7, 16-66)	30.4 (SD=7.59, 20-56)	30.4 (SD=7.39, 18-52)
EL-Atyp (n = 21)	474	183 (SD = 70.4, 101-364)	54.9 (SD=18.4, 26-94)	57.8 (SD=16.6, 30-90)	32.9 (SD=9.8, 16-56)	33 (SD=9.69, 21-59)	32.08 (SD=6.82, 21-44)
EL-ASD (n =14)	446	211 (SD = 68.2, 97-361)	48.8, (SD=15.8, 25-76)	49.4 (SD=17.9, 22-75)	28.7 (SD=10.2, 13-46	28.68 (SD=8.2, 20-43)	29.93 (SD=7.57, 20-44)

The number of good trials per participant was entered into a one-way (3 x 4; Condition (Standards 1,2,3) vs. Group (TL, EL-TD, EL-Atyp, EL-ASD) ANOVA. It revealed no group differences between the number of trials that were retained for wavelet analysis (all *p*s>.05). Number of trials was also co-varied with the observed habituation effect. The Stimulus order *x* Group interaction remained significant when taking into account the trial numbers ($F(1,57)= 3.99$, $p=.05$, $\eta^2 =.065$). There were no group differences between trial numbers for the Deviant conditions.

5.3 Results

5.3.1 Habituation.

5.3.1.1 ERP analysis (P150): Typical Likelihood Group.

Raw EEG signal was processed in NetStation (V.4.5.6) based on the pipeline described in Chapter 2.4 EEG pre-processing, and Chapter 4 (Guiraud et al., 2011; Seery et al., 2014; Webb et al., 2013). Grand average waveforms were exported to produce ERP plots (Figure 5.1). A repeated-measures ANOVA was carried out in the TL group with Condition (Standard 1 vs. Standard 3), ROI (frontal vs. tempo-parietal) and Laterality (right vs. left hemisphere) as repeated factors and P150 amplitude (averaged over 150-300ms) as a dependent variable. The model revealed only one main effect of ROI, with significantly higher P150 amplitude in the frontal than tempo-parietal regions ($F(1,12)= 8.13$, $p=.015$, $\eta^2 =.4$), although this effect did not persist after being controlled for Trial number ($p=.164$, $\eta^2 =.002$). Due to this, analysis of outcome groups was run for both ROIs and hemispheres.

5.3.1.2 ERP analysis (P150): Elevated Likelihood ASD Group comparisons.

The repeated measures ANOVA was repeated as above, with Group (EL-TD vs. EL-ASD) added as a between-subjects factor. The model showed a main effect of ROI ($F(1,63)= 102.3$, $p<.001$, $\eta^2 =.61$) and Laterality ($F(1,63)=20.39$, $p<.001$, $\eta^2 =.24$), with higher P150 amplitude overall in frontal regions and the left hemisphere. No interaction terms were observed. The between-group effect was not significant ($p=.17$, $\eta^2 =.003$). However, when trial numbers were introduced as a covariate, Group and Laterality effects failed to reach significance (all ps $>.06$).

5.3.1.3 Wavelet analysis (20-40Hz, 40-60Hz): Typical Likelihood Group.

A paired-samples *t*-test was carried out to examine reductions in amplitude of evoked gamma between the first and third repetition of each standard tone (Standard 1 vs. Standard 3) over left and right tempo-parietal regions in the two frequency bands respectively. This indicated a significant decrease in high (40-60Hz) gamma amplitude (habituation) over the right tempo-parietal region ($t(13)=2.58$, $p=.023$, $\eta^2=.35$) but not the left ($t(13)=-.65$, $p=.527$, $\eta^2= .034$); with no significant differences in the 20-40Hz band (ts < 1.6, ps >.54). Corresponding analyses over frontal ROIs revealed no significant effects across either gamma band (ts < 1, ps >.21).

5.3.1.4 Wavelet analysis (40-60Hz): Elevated Likelihood ASD Group comparisons.

Based on the pattern of findings in the TL infant group, analysis of ASD outcome was constrained to the 40-60Hz frequency band over the right tempo-parietal region. A one-way ANOVA revealed an effect of group on Standard 3 – Standard 1 difference scores ($F(1,55)=6.67$, $p=.012$, $\eta^2=.105$); which remained significant after controlling for Trial number ($F(1,55)=6.53$, $p=.013$, $\eta^2=.105$). Specifically, there was a decrease in gamma activation between the first and third repetition in EL-TD, relative to an increase in the EL-ASD group. Figure 5.2 shows the responses for the three groups with respective scalp maps to show approximate distribution of activity. Removal of EOG electrode activity did not change model effects, suggesting that the observed effects were not due to ocular muscle activity (Kampis, Parise, Csibra, & Kovács, 2016; Appendix J). Additionally, the main effect of group persisted when the EL-Atyp group was included in the model (Appendix H).

5.3.1.5 ITC: Elevated Likelihood ASD Groups.

For this analysis, all Standard trials were collapsed to increase signal-to-noise-ratio, and the analysis was focused within the same ROI where differences were reported in the EL group

(right tempo-parietal electrode cluster). A univariate ANOVA was used to examine group differences in the alpha-beta band (10-20Hz). This revealed significantly *greater* ITC in the EL-ASD than the EL-TD group ($F(1,55)=4.62$, $p=.036$, $\eta^2=.06$); which remained significant when controlled for Trial number ($F(1,54)=4.58$, $p=.037$, $\eta^2=.06$). When the EL-Atyp group was included, there were no significant differences in ITC across the three groups (see Appendix H for further details).

5.3.1.6 Cortical reactivity index (CRI).

In an exploratory analysis between cortical indices of reactivity and phenotype, a composite CRI was created by computing *z*-scores for the 40-60Hz evoked gamma and 10-20Hz ITC responses for the whole sample, which was then averaged across the two indices. Note that the index was not calculated for responses to Change Detection (see 5.3.2), primarily due to significantly smaller trial numbers. A higher score on the CRI would reflect diminished auditory habituation. An ANOVA indicated significantly higher CRI scores in the EL-ASD than EL-TD group ($F(1,55) =15.16$, $p<.001$, $\eta^2=.22$). When the whole sample was included, the main effect of group remained significant, and EL-ASD infants maintained significantly higher CRI scores than TL, EL-Atyp and EL-TD groups (*p*s between .002-.045).

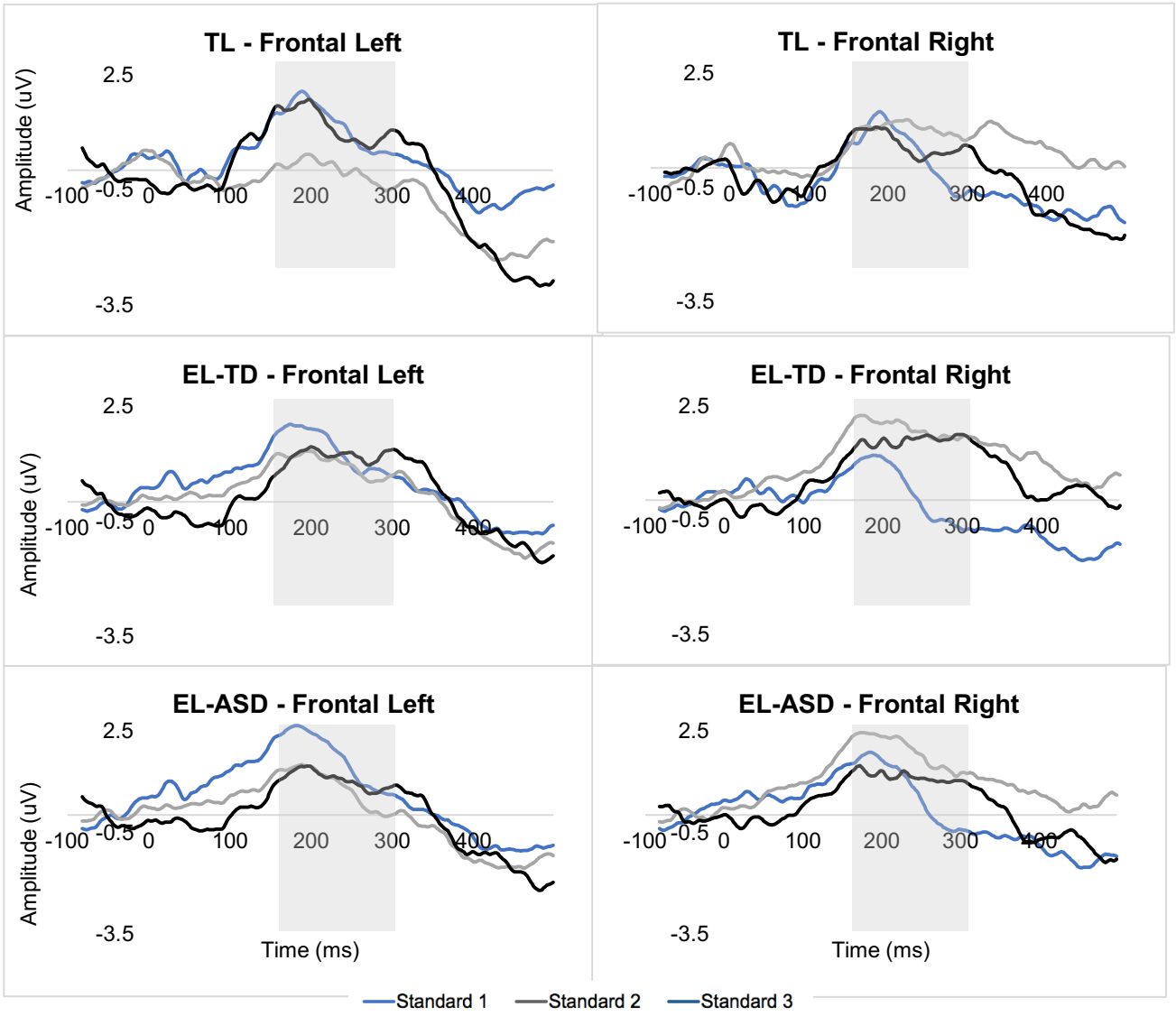


Figure 5.1 Event-Related Potential (ERP) figures for the three repetitions of the Standard tone in the right and left frontal clusters, where a significant P150 difference was observed relative to the tempo-parietal region. No significant differences were observed between the first and third repetition of the Standard, nor between participant groups.

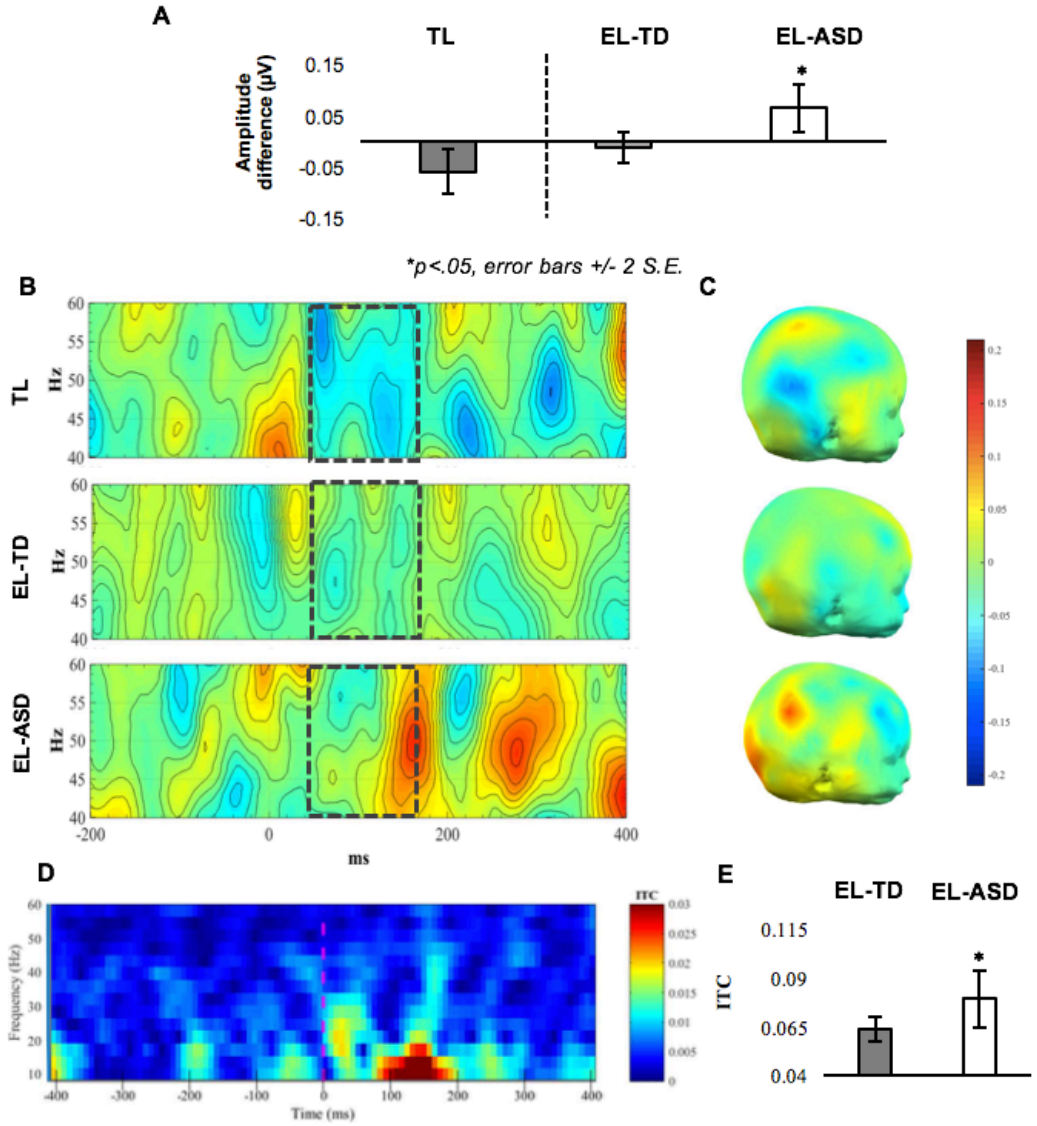


Figure 5.2 **(A)** Amplitude difference of 40-60Hz evoked gamma in the right tempo-parietal electrodes between Standard 3 and Standard 1. **(B)** Difference plots of the gamma responses to the repetition of standard tone (Standard3-Standard1) 40-60Hz evoked gamma in right tempo-parietal electrodes. TL group show a clear repetition suppression, the EL-ASD group show an increase in gamma activation. **(C)** 3D Scalp maps of the difference in 40-60Hz gamma activation between Standard 3 and Standard 1 over 100-150ms. **(D)** Total ITC responses collapsed across all infants and Standard trials over100-180ms time-window and 10-20Hz. (E) ITC for all standards collapsed together for the infant sibling groups from right tempo-parietal scalp region. TL group included for reference.

Note. Error bars depict standard error of the mean for each group respectively. Adapted from Kolesnik and colleagues (2019).

As shown in Figure 5.3, the CRI composite score was also significantly associated with developmental changes in Receptive Language between 8 and 36 months across all infants in the sample (r(88)=-0.25, p=.032, *CI*[-0.23 0.18]); controlling for trial number (r(88)=-0.26, p=.03, *CI*[-0.23 0.18]), and SRS™ Total t-scores (r(88)=0.22, p=.04, *CI*[0.01 0.41]); controlling for number of trials(r(88)=0.22, p=.039, *CI*[0.01 0.41]), but not with change in Expressive Language (r(85)=-0.17, p=-0.20, *CI*[-0.36 0.44]); controlling for trial number (r(85)=-0.12, p=.27, *CI*[-0.32 0.09]). No significant association was found between scores on the index and the ADOS severity scores (r(88)=.15, p=.162, *CI*[-0.06 0.34]); controlling for trial number (r(85)=0.16, p=.135, *CI*[-0.05 0.36]).

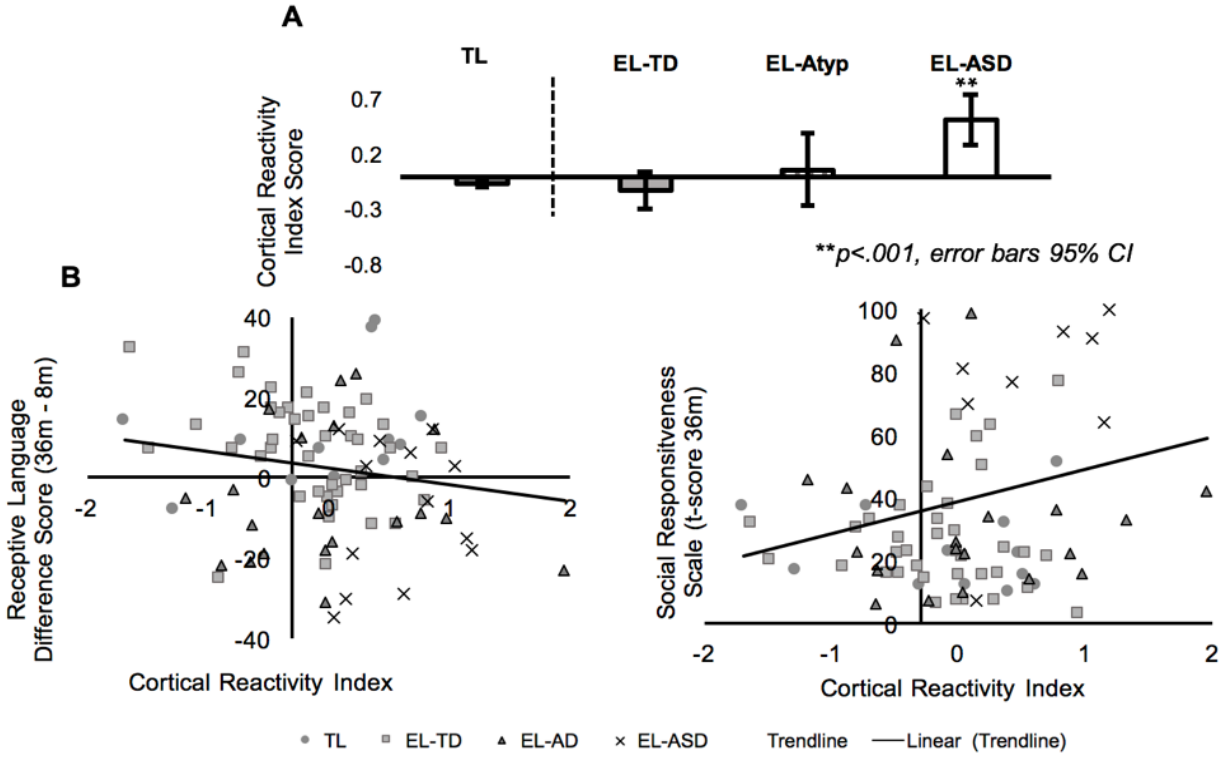


Figure 5.3 – **(A)** CRI z-scores for all groups (i.e. composite score for difference in evoked gamma (40-60Hz) and ITC responses (10-20Hz) over right tempo-parietal ROI). CRI was associated with **(B)** smaller change in Receptive Language scores between 8 and 36 months and **(C)** higher SRS™ scores, a dimensional measure of ASD-related traits. Note. The fit line is for an average of all infants. Error bars depict standard error of the mean. Adapted from Kolesnik et al. (2019).

5.3.2 Change Detection.

5.3.2.1 ERP analysis (MMN, P3a): Typical Likelihood Group.

Next, deviance detection within the ERP response was investigated between the Standard tones (Standard 1-3) and the Pitch and White Noise Deviants. A series of repeated-measures ANOVAs were carried out in the TL group with Condition (Pitch Deviant vs. Sum of Standards; White Noise vs. Sum of Standards), ROI (frontal vs. tempo-parietal) and Laterality (right vs. left hemisphere) as repeated factors and amplitude for the MMN (averaged 100-300ms) as well as the P3a (averaged over 200-400ms; He et al., 2007) components as separate dependent variables.

Analysis of the Pitch Deviant vs. Standard 1-3 revealed no main effects or interaction terms for the MMN (all *p*s .09-.8) and the P3a components (all *p*s .13-.88), which persisted when trial numbers were added as a covariate. The model to assess responses for the White Noise Deviant returned a significant effect of ROI for the MMN component ($F(14)=10.27$, p=.006, $\eta^2=.42$) as well as a significant Condition x ROI interaction ($F(14)=2.88$, p=.044, $\eta^2=.25$). Follow up analyses showed higher amplitude in Frontal ROI for the White Noise Deviant than the sum of Standard tones ($t(13)=-2.17$, $p=.047$, $r=.51$; Figure 5.4), which remained after controlling for trial number. These effects remained significant once trial numbers were added as a covariate, as well as an added main effect of Laterality ($F(13)=6.23$, $p=.023$, $\eta^2=.33$), with higher responses in the right than the left hemisphere, although no significant effects were revealed in follow up tests ($p=.442$). For the P3a response to White Noise, there was a significant main effect of Condition ($F(14)=5.49$, $p=.034$, $\eta^2=.28$) and ROI ($F(14)=5.44$, $p=.035$, $\eta^2=.28$) as well as a Condition x ROI interaction ($F(14)=6.39$, $p=.024$, $\eta^2=.31$). Follow up effects showed elevated P3a response in the frontal region for the White Noise vs. Standard tone ($F(13)=6.23$, $p=.023$, $\eta^2=.33$). With trial numbers added, these effects

did not persist, while an effect of Laterality emerged ($F(13)=7.4$, $p=.017$, $\eta^2=.36$), as well as a Condition x Laterality effect ($F(13)=9.64$, $p=.008$, $\eta^2=.42$), showing higher responses in the frontal right ROI.

5.3.2.2 ERP analysis (MMN, P3a): Elevated Likelihood ASD Groups.

Based on results from the TL group above, MMN and P3a components were compared in the frontal ROIs between EL-ASD and EL-TD groups. For Pitch Deviant, in the MMN temporal window, there was an effect of Condition ($F(55)=13.85$, $p<.001$, $\eta^2=.202$) and Laterality ($F(55)=14.53$, $p<.001$, $\eta^2=.209$). There was also a Condition x Laterality ($F(55)=16.05$, $p<.001$, $\eta^2=.23$) interaction. Follow up analyses revealed that the effect was driven by higher average amplitude of response to the Pitch Deviant in the Frontal Right ROI ($t(56)=-5.02$, $p<.001$, $r=0.55$). There was no significant difference in response between EL groups ($p=.45$, $r=0.1$). However, effects reported above did not survive post-hoc adjustment for Trial number. For the P3a component, there was a Laterality x Group interaction ($F(56)=5.28$, $p=.025$, $\eta^2=.086$), which remained significant when trial numbers were added to the model. Follow up independent samples *t*-test revealed higher P3a amplitude in the left hemisphere of the EL-ASD group, but this was not statistically significant ($p>.08$; Figure 5.4).

For the White Noise Deviant, there was only an effect of Condition ($F(56)=7.55$, $p=.008$, $\eta^2=.119$), with higher amplitude in the MMN temporal window for the Deviant than the Standard tones. For comparison of P3a component, there was also an effect of Condition ($F(56)=10.43$, $p=.002$, $\eta^2=.157$), with higher amplitude of response for the White Noise stimulus. Effect of Condition did not persist when Trial number was added as a covariate ($p=.07$, $\eta^2=.05$).

5.3.2.3 Wavelet analysis (20-40Hz, 40-60Hz): Typical Likelihood Group.

Similarly to the habituation analysis described above, two paired-samples *t*-test were carried comparing evoked gamma between the sum of Standard tones vs. (1) Pitch Deviant and (2) White Noise Deviant, over left and right tempo-parietal regions in the low and high frequency bands respectively in the TL group. Significant reduction between the Standards and the Pitch Deviant were revealed for 20-40Hz gamma in the Frontal right ($t(17)=-2.64$, $p=.017$, $r=0.56$) and the Tempo-Parietal right ($t(17)=-2.25$, $p=.038$, $\eta^2=.5$) ROIs, but no differences in high gamma. For the White Noise Deviant, no significant differences were revealed in the TL group.

5.3.2.4 Wavelet analysis (20-40Hz): Elevated Likelihood Group.

For analysis of responses in the EL-ASD and EL-TD groups, differences in amplitude of low gamma to both Pitch and Vowel deviants were examined in the right Frontal and Tempo-Parietal regions. A one-way ANOVA was carried out on the difference score between the Deviant conditions and Sum of Standards and revealed no significant differences between groups nor ROIs. As no group effects were found in this analysis, behavioural comparisons were not carried out.

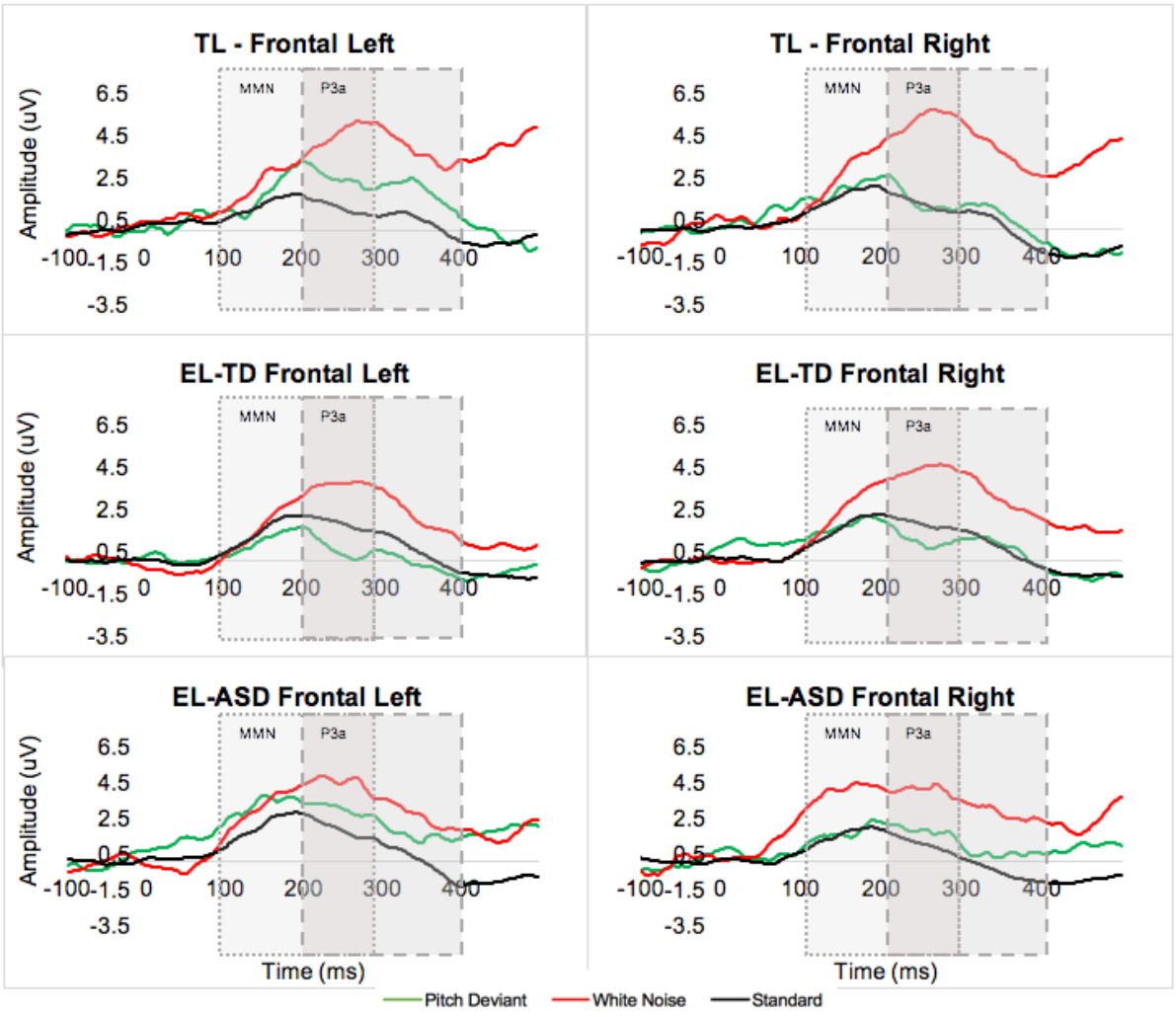


Figure 5.4 Event-Related Potential (ERP) figures for the Change Detection responses (Sum of Standards, Pitch Deviant, White Noise Deviant). Significant increases in amplitude were observed for MMN and P3a components in this sample across all outcome groups, although heavily influenced by number of 'good' trials. *Note.* The narrow-dashed region represents the time-course of the MMN response (100-300ms) and the wide-dashed region captures the P3a (200-400).

5.4 Discussion

The present investigation showed evidence of atypical neural responses to auditory repetition and change in infants with later ASD, prior to the emergence of behavioural symptoms. The findings are consistent with the idea of altered neurotransmitter function in infancy as a potential pathway to ASD (Rubenstein & Merzenich, 2003). In this experiment, infants with later ASD showed reduced habituation response through evoked gamma activity as well as elevated 10-20Hz phase locking present as early as 8 months of age. As an additional exploratory step (Ethridge et al., 2016), a combined 'cortical reactivity' index was dimensionally associated with reduced development of receptive language abilities as well as social communication at 3 years across the whole cohort. In contrast to previous literature and the predictions set out at the start of this investigation, no reliable differences in gamma activity were observed for responses to auditory oddballs. There were no group differences in ERP responses to repetition or auditory change, which was evaluated below relative to existent literature. The findings suggested that oscillatory activity in response to repetition may be considered a predictive marker of language functioning difficulties. As auditory reactivity was previously linked to weakened GABA circuitry in infant mice (Gogolla et al., 2009, 2014), atypical responses to repetition could suggest a lack of regulation within the E/I functioning in infants with later ASD.

5.4.1. Implications of atypical habituation response in ASD.

One possible mechanism of atypical responses to repetition of sensory stimuli is disruption of experience-dependent specialisation in the brain, as the inhibitory signals critical for habituation are also critical in shaping sensitive periods in early development (Hensch, 2005; Yizhar et al., 2011). Altered trajectories of specialisation are an emerging theme from prospective infant sibling studies, where infants with later ASD have shown a decline in interest in eyes and faces across the first year of life (Jones & Klin, 2013) as well as slowed

attention-shifting (Elsabbagh, Fernandes, et al., 2013) and early signs of language delays (Mitchell et al., 2006; Webb et al., 2013). Such behavioural changes are related to alterations in specialised brain activity. For example, between 5 and 6 months, infants with later ASD were reported to have reduced sensitivity over temporal cortex to human sounds (Blasi et al., 2015; Lloyd-Fox et al., 2013) and altered event-related potential responses to pictures of faces (Elsabbagh et al., 2012; Webb et al., 2011). In the present task, exploratory CRI was related to dimensional variation in receptive language growth between 8 and 36 months, an age-range associated with specialisation of language regions (Dehaene-Lambertz, 2000).

Elevated cortical reactivity may emerge from a range of impairments at the molecular level, contributing to reduced inhibition or increased excitation. Select environmental risk factors may have converging effects through oxidative stress, which is thought to impact parvalbumin inhibitory interneurons. This is thought to be a key mechanism for regulation of E/I balance (Hu et al., 2014; Yizhar et al., 2011), and form a unified pathway for emergence of neurodevelopmental conditions, including ASD and schizophrenia (Richetto et al., 2014; Steullet et al., 2017). Selten and colleagues (2018), for example, showed that inhibitory system dysregulation in the cortex and hippocampus had detrimental effects on signal processing and later phenotypic changes associated with psychiatric and neurodevelopmental conditions (Selten et al., 2018). Recent work with knock-out models of ASD (including mice models of Fragile X) implicated early increases in spontaneous synchronous activity and upregulation of synaptic turnover in sensory cortices as a common phenotype, consistent with excess cortical reactivity (Gonçalves, Anstey, Golshani, & Portera-Cailliau, 2013; Isshiki et al., 2014). In human adults with Fragile X syndrome, reduced habituation of neural responses to tones was associated with elevated gamma at baseline (Ethridge et al., 2016). In animal models, atypical cortical reactivity was normalised by administration of $GABA_B$-receptor agonist arbaclofen

(Gandal et al., 2010), which suggested that pharmacological manipulation studies and their effect on gamma activity may be fruitful in translational research.

Results from the oddball task further complemented previous findings of altered habituation mechanisms in ASD. Reduced habituation of ERP responses has been observed in a subsample of the present cohort of EL infants (Guiraud et al., 2011) and repetition of speech sounds in other samples (Seery et al., 2014). In the visual domain, toddlers with ASD showed delayed adaptation to repetition, particularly to social stimuli (Webb et al., 2011), while adults showed diminished habituation responses with increasing levels of ASD traits (Ewbank et al., 2015). Habituation is a critical process by which the brain devotes resources to novel and unexpected stimuli. Atypical/reduced habituation is therefore likely to affect the efficacy with which the brain encodes complex stimuli, such as language, which rely heavily on focusing attention on important dimensions of change in auditory signals (Arimitsu et al., 2011; Edgar et al., 2013). Atypical habituation could also contribute to exaggerated sensory sensitivities observed in children with ASD (Orekhova et al., 2008), as well as delayed language ability, a strong predictor of developmental outcomes in individuals with ASD (Pickles, Anderson, & Lord, 2014; Szatmari, Bryson, Boyle, Streiner, & Duku, 2003). Future longitudinal research is required to determine whether the observed alterations in cortical reactivity represent a developmentally pervasive phenomenon, or a transient developmental delay in the normal increases in inhibitory activity observed in early infancy (Dorrn et al., 2010; Rubenstein & Merzenich, 2003). Assessment of individual stability and test-retest of these reponses would alter the expression of excitatory/inhibitory processing over developmental time (Dorrn et al., 2010; Lee et al., 2016; Nelson & Valakh, 2015).

5.4.2 Implications of the 'typical' change detection response in ASD.

There were no group differences in gamma activation in response Pitch or White noise deviants, which challenged previous reports (Guiraud et al., 2011). Language acquisition is

dependent on attention to novelty and change, which questions generalisability of the findings. One possible explanation for this finding is the nature of the stimuli used (i.e. simple tones and white noise). ASD-specific atypicalities have been reported in the processing of speech vs. non-speech sounds (Čeponienė et al., 2003; Lepistö et al., 2005) as well as naturalistic speech (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson et al., 2004; Kuhl, Coffey-Corina, Padden, & Dawson, 2005). Language stimuli, i.e. vowel sounds used in Chapter 4, may be more likely to elicit robust group differences between typically developing infants and those with later ASD. Another potential explanation is that if infants with elevated likelihood of ASD are not forming adequate precepts of the repeated stimuli (He et al., 2007), they were not able to produce a sizable response once the stimulus changes. However, a more likely explanation was that small sample sizes as well as smaller trial numbers of both deviant stimuli categories did not detect responses to auditory change.

Analysis of ERP components did not reveal expected group differences, and indeed showed a large positive-going peak which extended over the regions where both the MMN and the P3a components (100-400ms) were expected. The observation was in contrast with previous findings, where a significant MMN response was observed in new-borns and 3-month-old infants (Cheour, Leppänen, & Kraus, 2000; Cheour-Luhtanen et al., 1995; Lepistö et al., 2005). There is, however, a considerable debate about the validity of the change detection response. A positive ERP response has also been observed following deviant stimuli (Leppänen et al., 1997), which has been subsequently replicated and defined as the positive mismatch response (pMMR; Maurer, Bucher, Brem, & Brandeis, 2003; Näätänen, Gaillard, & Mäntysalo, 1978; Seery et al., 2014). Since, there have been several hypotheses about the nature of this component and its functional significance. Maurer and colleagues (2003) suggested that the pMMR is an inverted MMN response, although very little is currently known about the possible underlying mechanisms behind this inversion.

It should be noted that there are considerable maturational factors at play in the generation of an ERP response (Čeponienė et al., 2009; Čeponienė et al., 2004; Kushnerenko et al., 2002; Kushnerenko, Bergh, Bea, & Winkler, 2013). Kushnerenko and colleagues (2002) conducted a longitudinal EEG study with infants across the first two years of life and found large individual variability in the presentation of the MMN component across all age groups, as well as a large-positive going ERP component at 9 months, which they argue was a protracted P3a response that was 'masking' the MMN. It should also be noted that infants in Kushnerenko's study were only selected for analysis if they presented with the MMN response (~75% sample at each time point), which was not set as a criterion in the present investigation.

Lastly, differences in processing of the signal can explain inconsistencies across the MMN response in previous literature and present task. Specifically, He and colleagues (2007) used different band-pass filter settings when processing responses of 2-, 3- and 4-month-old infants to tones and found that more aggressive filtering of 3-20Hz revealed an adult-like MMN in most scalp regions by 3 months of age, whereas a 0.5-3Hz filter setting revealed a slow positive wave in the same sample. Although several factors may be used to explain why there were no differences observed in change detection responses between infants with and without later ASD, differences in band-pass filtering approaches and inclusion criteria should be taken into account when evaluating infant MMN literature.

5.4.3 Conclusion

Overall, findings of the present task revealed reduced auditory habituation in infants with later ASD. I further proposed candidate mechanistic pathways underlying this response, by linking alterations in gamma to individual level differences in later language and social functioning. Future work may consider whether these responses remain stable over time, or change dynamically through the course of development. Although no group differences were

observed in presentation of ERP responses or responses to auditory change, several possible explanations were considered to explain inconsistencies with existing infant literature.

Chapter 6. Auditory Steady-State Responses in Infants with Familial Likelihood of Neurodevelopmental Disorders and Neurofibromatosis Type 1

Results of Chapter 5 supported existent literature, which argued that gamma-band oscillatory activity may be an important endophenotype to identify early presentation of ASD. This argument is further substantiated by findings of the relationship between brain connectivity and gamma activity (Ahnaou et al., 2017; Freeman, 1975) as well as the relationship between gamma and GABAergic transmission (Balz et al., 2016). Although some interesting differences in gamma activity were observed in response to stimulus repetition, there are several ways in which this neural oscillation can be assessed. The nature of the gamma or *y*-band responses are complex and multifaceted, as outlined by Rojas and colleagues (2011). As well as a transient, highly phase-locked response that occurs from 30ms after stimulus onset, modulating the frequency of an auditory stimulus (i.e. through trains of clicks or regulated change in frequency) produces a characteristic Auditory Steady-State Response (ASSR; (Azzena et al., 1995).

Although the ASSR has been commonly used to measure hearing thresholds in infants and children (Oliveira et al., 2014), the strength of this response can provide information about the function of the auditory cortex beyond passive perception (see Chapter 5). Specifically, ASSR is an electrophysiological response that is entrained to the frequency and phase of the stimulus. The response is generated by the auditory pathway and auditory cortex activity and postulated to be dependent on activity at the excitatory NMDA receptors. In this way, atypicalities within the ASSR may be an index of early disruption to the E/I balance, with downstream effects on auditory processing and communication (Rojas et al., 2011; Wilson et al., 2007). The response may be particularly useful as a translational biomarker due to potential

pharmacological interventions that have been used to restore a 'typical' ASSR in human and mouse models (Ehrlichman et al., 2009; Krystal et al., 1994; O'Donnell et al., 2013; Pinault, 2008).

It was therefore important to establish whether ASSR is sensitive to atypical developmental trajectories, during key stages of E/I balance development (see Chapter 6.1.2). One challenge is that some studies have demonstrated considerable difficulty in obtaining reliable ASSR responses in children and younger populations (Edgar et al., 2016; Maurizi et al., 1990). The present investigation was therefore designed as a feasibility study of measuring ASSR in awake infants, as well as the utility of this task in predicting variability within the phenotypic profile and diagnostic specificity (i.e. is atypical ASSR prevalent across several neurodevelopmental disorders in the same way or are there differences in this response that can be used to help predict outcome). The following study addressed two important aims. Firstly, it was investigated whether 40Hz ASSR (i.e. higher response over the gamma band in response to 40Hz stimulation frequency/repetition rate) can be observed in infants at 14 months of age. Then, the specificity of 'atypical' ASSR in ASD was examined, by comparing the differences or an interaction with the response to that of infants with family history of ADHD or between neurotypical infants and those with a genetic disorder NF1 (which has elevated prevalence of ASD and ADHD in the phenotype, see Chapter 1.6.2.1).

Data presented in this chapter has been collected between 2012-2019 as part of the Studying Autism and ADHD Risks project (STAARS; https://www.staars.org/) as well as between 2014-2019 for EDEN study (http://research.bmh.manchester.ac.uk/socialdevelopment/eden, a portion of which has been described in Chapter 4) by the researcher team at CBCD, Birkbeck College. Data collection is still underway and outcome data/number of infants presented below represents a subset of the total recruited so far for each individual project (stopping rule for the first 'data freeze' in

STAARS in June 2017 and mid-July 2019 for the EDEN study). My contribution to this dataset has been data collection (2015-2019), as well as pre-processing and analysis of demographic, behavioural and electrophysiological data. The data discussed has not been featured in any other work.

6.1 EEG Task 3: Feasibility Study of ASSR in Infants and Sensitivity of the Response to Alternative Developmental Trajectories.

In support of the E/I imbalance theory (see Chapter 1.6.1, Chapter 5.1), recent imaging findings reported atypical short and long-range connectivity and disrupted gamma brain rhythms in individuals with ASD (30-80Hz). As highlighted previously, gamma rhythms are the most widely researched and understood in the human brain and have been recognised as a marker attention and top-down processing, as well as integration of sensory information, known as perceptual binding[29] (Gray, 1994; Gray & Singer, 1989). The amplitude of neural activity, however, is directly proportional to frequency, which means that the signal from gamma-band activity is very small and is more difficult to record relative to alpha or theta. Low levels of detectable activity in the gamma band could potentially explain the inconsistencies in the ASD literature on gamma and E/I balance (Dickinson et al., 2016). One of the ways in which neural responses within higher amplitude frequencies can be strengthened is by 'driving' gamma networks through presentation of frequency modulated stimuli (Legget

[29] In sensory processing research, Perceptual Binding is defined as a process of merging individual segments of sensory information into coherent representations that are meaningful in the context (i.e. individual sounds are perceptually bound into meaningful segments, words; with similar processes occurring across other types of sensory information, including vision, where mouth movements are bound to incoming sound information, that is perceived as speech; (Stevenson et al., 2014; Stevenson & James, 2009).

et al., 2017). An additional complication is that gamma-band activity occurs within the same frequency band as muscle artefact, which affects both the recording and interpretation of the results (Criswell, 2011; O'Donnell, Berkhout, & Adey, 1974). The use of auditory paradigms, however, may minimise the likelihood of muscle artefact contamination as addressed in Chapter 6.4.1.

Firstly, I considered whether the adult and child literature on the ASSR is sufficient to support the paradigm as an EEG-based marker for atypical specialisation in neurodevelopmental disorders. Then, I explored the potential benefits and caveats in measuring the ASSR in infant populations. Due to the limited number of studies that looked at gamma function (and driving of the gamma response specifically) in infant literature, the study was designed to address several questions left open in the field as well as to evaluate cross-syndrome specificity of the response.

6.1.1 Auditory steady-state response overview

The ASSR has been defined as a basic neural response, which mimics the temporally modulated stimulus in frequency and phase, and is therefore suitable for examining the ability of the cortical network to generate and maintain oscillatory activity in a given frequency band. Stimulus frequency/repetition rate of around 40Hz has been reported to produce the largest ASSR in humans for both 40Hz click trains or amplitude-modulated tones, with a large right-sided lateralisation (Azzena et al., 1995; Boettcher, Madhotra, Poth, & Mills, 2002; Boettcher, Poth, Mills, & Dubno, 2001; Ross, Herdman, & Pantev, 2005; Stapells, Makeig, & Galambos, 1987; Wilding, McKay, Baker, Picton, & Kluk, 2011). It has since been suggested that activity within the gamma frequency range that is often centred around 40Hz represents the 'natural' resonance frequency of cortical networks.

There are important differences between the ASSR and the traditional measures of oscillatory activity (e.g. response to presentation of pure tones or presentation of simple visual stimuli). Specifically, driving a response with repeated clicks amplifies power around the modulation frequency, and it is more likely to detect robust responses within the respective frequency bands than measures of evoked/induced power in response to simple tones. Studies with typically developing adults and individuals with Schizophrenia found good test-retest reliability of ASSR gamma activity (McFadden et al., 2014; Roach et al., 2019). At the present time, there is limited evidence on the functional differences between 40Hz ASSR and spontaneous gamma band responses. Some authors further suggested that using the metrics together may be beneficial when exploring general deficits in neural synchrony (Presacco et al., 2010; Schuelert et al., 2018).

A single study to date has compared ASSR responses relative to traditional ERPs (L. Zhang et al., 2013). It was found that ASSR following different stimulation frequencies were generated by phase synchronisation rather than power enhancement and modulated by stimulus intensity rather than loudness, the opposite of which was true for transient ERPs. Importantly, ASSR and ERP responses demonstrated different scalp topographies that were not correlated with one another, which suggested that different mechanisms may be involved in their generation and propagation. Zhang and colleagues (2013) further argued that ASSR was likely to reflect auditory entrainment rather than the superposition hypothesis (i.e. that steady-state responses occur as a summation of successive transient ERPs; Tan, Yu, Lin, & Wang, 2015), and therefore the two measures may be used to study distinct neural mechanisms. In the present investigation, it was important to observe whether a distinct 40Hz ASSR could be detectable in infants and what are the differences in temporal and spatial locations of the ASSR versus the traditional ERPs or gamma-band responses outlined in Chapters 4 and 5.

6.1.2 ASSR: a translational biomarker for neurophysiological disorders?

Although the ASSR has been widely used to measure hearing threshold in difficult to test patient groups, over different stimulus repetition rates, its association with cognitive function has been implicated only recently (Rojas et al., 2011; Wilson et al., 2007). The majority of our understanding of the response comes from animal and human audiology work, which investigated the neural mechanisms and thresholds of the ASSR and has been sufficiently characterised (see: O'Donnell et al., 2013; Sivarao, 2015; Sullivan, Timi, Hong, & O'Donnell, 2015).

The ASSR has further been used to observe gamma-band atypicalities in neurodevelopmental conditions, including adults with ASD and as well as parents of children with ASD (Rojas et al., 2011; Rojas & Wilson, 2014). Specifically, a reduction in 40Hz ASSR was associated with deficit in social skills, which had lead researchers to suggest that it may be a useful biomarker of atypical functional specialisation in the brain and ASD outcome. In the context of these studies, Rojas and colleagues (2011) reported robust effects of ASSR abnormalities relative to evoked responses in adult participants.

However, there have been inconsistencies reported in ASSR literature in child populations. While some studies have reported that reduced 40Hz ASSR associated with ASD diagnosis (Wilson et al., 2007), others did not find differences between the typically developing group and individuals with high-functioning ASD (Edgar et al., 2016). Inconsistencies across studies may be attributed to differences in sample size or analysis techniques and are further considered in relation to younger populations in Chapter 6.1.2.

In addition, abnormalities within the gamma-band and the ASSR may not specific to ASD, and have been reported across several neurodevelopmental conditions. This was substantiated by extensive literature on atypical ASSR in individuals with Schizophrenia (SCZ;

Brenner, Sporns, Lysaker, & O'Donnell, 2003; Hall et al., 2011; Lenz, Fischer, Schadow, Bogerts, & Herrmann, 2011; O'Donnell et al., 2013; Thuné, Recasens, & Uhlhaas, 2016). Although there is considerable overlap between SCZ and ASD in their clinical presentation including social dysfunction and sensory atypicalities, there are clear differences in the behavioural phenotype and developmental timing of the emergence of symptoms. There has been some evidence from animal and post-mortem studies that found atypical glutamatergic and GABAergic circuit dysfunction in both disorders, and both ASD and SCZ emerge during periods of high plasticity and change in the brain (see Gao & Penzes, 2015). Extending the study design to look at similarities/differences within the ASSR across different developmental or genetic conditions was done in the present study to examine specificity of the ASSR in infants.

6.1.2.1 Motivation for participant selection.

It has been suggested that ASSR may be a general metric of atypical brain development and reflect electrical oscillatory deficits present across many conditions, which substantiated present animal research (Kozono et al., 2019; Vohs et al., 2010; Wang, Ma, Wang, & Qin, 2018). Based on this evidence, a population of infants with family history of Attention Deficit Hyperactivity Disorder (ADHD) was investigated in addition to infants with elevated familial likelihood of ASD. ADHD is characterised by inattention, hyperactivity and impulsivity (see Chapter 1.5.2 for incidence rates and justification for use of this group in infant sibling design). Typically, ADHD is diagnosed by a clinician around 5-7 years of age, as children enter school (although there is evidence of early manifestations of ADHD before behavioural symptoms emerge; Johnson, Gliga, Jones, & Charman, 2015). The condition's heritability rates vary between 77-88% (Faraone & Larsson, 2019); with significant co-morbidity with ASD (Russell et al., 2014). Several studies have shown evidence to support atypical glutamatergic and GABAergic signalling in brains of children with ADHD, and therefore may represent

similarities with the ASSR (Edden et al., 2012; Spencer et al., 2014). More recently, reduced ASSR over the right hemisphere has been reported in adolescents with ADHD relative to age-matched typically developing controls (Khaleghi et al., 2019).

Additionally, ASSR was investigated in infants diagnosed with NF1 (see Chapters 1.6.2.1 and 4.1.4). As atypical E/I balance has also been observed in NF1 patients (Violante et al., 2013) and atypical 40Hz ASSR was found in adolescents and young adults with 22q11.2 Deletion Syndrome (Larsen et al., 2018), a cross-diagnostic approach was used to investigate the ASSR in NF1 and align with the RDoC framework criteria (Insel et al., 2010). Comparing group data based on familial/monogenic likelihood of developmental disorders was used to understand whether differences in response are syndrome-specific, or occur as a generic marker of alternative developmental pathways (see section 6.1.3 of this Chapter). Establishing atypical ASSR across several different infant groups with different levels of familial or monogenic likelihood of a neurodevelopmental condition may provide a sensitive marker of neural specialisation.

In the context of this investigation, ADHD and NF1 groups were included in order to examine whether gamma-band atypicalities were specific to (1) familial vs. monogenic likelihood of ASD/ADHD and (2) condition specific ASD vs. ADHD.

6.1.3 Advantages and challenges of measuring ASSR in infant populations.

Lastly, the functional significance of the ASSR response was evaluated in typical and atypical infant development, as well as the feasibility of using the response as a neural marker of specialisation. One of the biggest advantages of an auditory EEG paradigm, is it's the ease in administration in difficult-to-test populations. The ASSR has further shown good test-retest reliability in both EEG and MEG methods (Legget et al., 2017), as well as higher sensitivity to detect differences in first degree relatives than transient gamma responses that occur within

the first 50ms following stimulus onset (Rojas et al., 2011). Rojas and colleagues (2001) replicated previous studies to look at ASSR, phase-locking and transient gamma responses simultaneously and observed differences in 40Hz and 48Hz ASSR and phase-locking only. It was further found that the evoked activity was not robust across individuals (Michael J. Gandal et al., 2010; Rojas et al., 2011), which further emphasised the need to look at ASSR to compliment findings reported in Chapter 5.

An important aspect of the ASSR for the present investigation was its protracted development. Rojas and colleauges (2006) looked at 40Hz ASSR through MEG in participants 5-52 years of age and found an increase in amplitude of gamma driving response with age. The increase was predominant in childhood and early adolescence, after which the response appeared to reach a plateau. A further longitudinal study across two time points in late childhood supported these conclusions, as it was found that children showed bigger differences in gamma power following 40Hz ASSR stimuli between 10 and 11.5 years relative to changes in adult participants over the same time period (Poulsen et al., 2009). The ASSR has been reported to undergo dynamic changes across early infancy to adolescence, which supports its role as a marker of cortical specialisation, according to the predictions set out in Chapter 1. It has recently been found that ASSR was stable over testing time, and therefore more likely to be reliable measure in both research and clinical settings (Van Eeckhoutte et al., 2018).

However, there has been widely expressed difficulty in measuring ASSR in young infants and children, as several studies did not observe a significant 40Hz ASSR between 0-6 months (Maurizi et al., 1990; Stapells et al., 1987). One possible explanation is that responses to low stimulation frequency/repetition rates (~40Hz) are affected by sleep and sedation, with several research groups failing to detect a reliable 40Hz ASSR peaks in adults and infants during sleep (Dobie & Wilson, 1998; Edgar et al., 2016; Stapells, Galambos, Costello, & Makeig, 1988). In adult subjects, the ASSR ‘peak’ shifted from 40Hz in the awake state to

50Hz and 90Hz during sedation (Dobie & Wilson, 1998). Several studies argued that modulation frequencies in excess of 60Hz were required to minimise effects of sleep and sedation in infants and children (Aoyagi et al., 1994; Cone-Wesson, 2008; Lins et al., 1995; Picton, 2011; Picton et al., 2007; Stapells, 2001). It was further suggested that 40Hz ASSR was most stable during the awake state only and that participant vigilance should be monitored during the testing period (Pethe et al., 2001).

Nonetheless, one study of anaesthetised infants looked at both ASSR from a frequency modulated paradigm and narrow-band chirps (Mühler et al., 2014), and reported adequate response thresholds from infants and children under the age of 2 years in both paradigms. Authors argued that previous infant studies used a small number of trials/short acquisition times that may have affected the strength of the ASSR. Another group found stronger responses to 40Hz than 80Hz stimulus frequency in a sample of 12 children (Tlumak et al., 2012) that was comparable to findings from young adults. Authors argued that any difficulty in obtaining a robust 40Hz ASSR in infants and young children was due to differences in task design and analytic protocols.

In addition, a study by Ross and colleagues investigated effects of modulation frequency on ASSR in human adults using frequencies ranging 10-100Hz using MEG and found maximum source amplitude responses to 20Hz and 40Hz stimulus frequency and minimal source amplitude responses at 10, 30 and 100Hz stimulus frequency (Ross, Borgmann, Draganova, Roberts, & Pantev, 2000). Taken together, these findings provided important information for the design of the paradigm, where the paradigm design to maximise trial numbers, as well as the choice of 20Hz (beta) and 40Hz (gamma) as contrast modulation frequencies. In addition to what is currently known about gamma band activity and cognitive function (see Chapters 1.6.4.1 and 2.2.3), beta activity has been associated with sustained attention in infancy and later language and attentional engagement function (Pratt et al., 2018;

Weiss & Mueller, 2012; Xie et al., 2017) and was therefore selected as a frequency of interest in the task. Although the evidence on the nature of the ASSR in awake infants is inconsistent, the wealth of animal and adult human research on sensitivity of the response to neurodevelopmental outcome warrant further exploration in a feasibility study.

6.1.4 Present study.

In order to address gaps in the literature, a frequency modulation task using 20Hz and 40Hz click-trains was carried out with infants at 14 months of age. 40Hz ASSR has been observed as the maximal response frequency in awake participants across several age groups. The 20Hz click train was used as a comparison, as higher responses may be recorded in the beta frequency band, and where no gamma activation was expected. The age-point was chosen to investigate differences in auditory cortex function after the initial functional specialisation of the auditory cortex as well as establishment of the E/I balance are thought to have taken place in typically developing individuals (i.e. in the first 12 months of life; Dorrn et al., 2010; Yizhar et al., 2011). Due to the number of different participant groups in this analysis and comparisons between familial likelihood of ASD/ADHD or ASD and ADHD as well as infants with NF1, only one age point was investigated.

The task was used to as a proof of principle that a robust 40Hz ASSR can be obtained from awake infants within the gamma power range, while higher power of response in the beta band was expected following 20Hz ASSR. It was further predicted that infants with increased familial likelihood of ASD or ADHD would show reduced gamma power following the 40Hz click train condition relative to typically developing infants. No group differences were expected in the 20Hz ASSR. A combined likelihood of ASD and ADHD was expected to have an additive effect on this response (i.e. further reduction) relative to the typically developing group. Based on findings of neural synchronisation deficits and atypical *y*-band activity in mouse and human studies of Schizophrenia, ADHD and Fragile X (Ethridge et al., 2016, 2017;

Khaleghi et al., 2019; O'Donnell et al., 2013), it was expected that infants with NF1 would also show atypical 40Hz ASSR, (i.e. a reduction in power relative to typically developing infants). Atypical auditory habituation reported in infants with NF1 at 5 month of age (Chapter 4) and 8-month-old infants with later ASD (Chapter 5), served as further validation for using this group in the current analysis. For the purposes of simplicity within the present analysis, we focus on power within pre-selected frequency bands only (over 15-25Hz for 20Hz stimulus frequency and over 36-46Hz for 40Hz stimulation frequency). Similarly to the analyses described in previous chapters, gamma power that was found to be sensitive to group/condition effects was then associated with the behavioural phenotype, measured by a combination of early language, sensory sensitivity and early ASD-symptomology. It was expected that suppression of gamma power/atypical ASSR would be associated with poorer language ability and elevated ASD behaviours.

6.2 Methods

6.2.1 Participants.

Participants were 166 infants around 14 months of age (+/- 3 weeks; Table 6.1). 81 infants with familial ASD (EL-ASD), 29 infants with familial ADHD (EL-ADHD), of which 21 infants have both familial ASD and ADHD (EL-ASD+ADHD) as well as 27 typically developing infants (TL). In 8 infants, familial diagnostic status has not been provided and they are excluded from present analysis. Participants were recruited for a longitudinal study running from 2012 to 2019 as part of the STAARS study.

Children with an elevated likelihood of ASD recruited for this study have at least one full sibling with a community clinical diagnosis of ASD. Additionally, infants with family history of ADHD were also recruited – all children have at least one first degree family member (sibling and/or parent) with a community clinical diagnosis of ADHD or a probable research

diagnosis of ADHD. Each infant in the study was assigned a rating for familial likelihood of ASD and ADHD. A rating of 1 for ASD indicates the presence of ASD in a parent or older sibling; a rating of 1 for ADHD indicates that presence of ADHD in a parent or older sibling; and a rating of 0 for either category indicates no confirmed presence of the relevant condition. Ratings were primarily based on the presence of a clinical diagnosis of ASD or ADHD. Thus, effects of ASD family risk will be examined based on effects of ASD (1=ASD, 0=noASD) or ADHD (1=ADHD, 0=noADHD) present in the family, as well as the interaction (i.e. in families where both ASD and ADHD are present; See Appendix K for classification information).

Infants with no history of developmental disorders were also recruited from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development. They had to have at least one older sibling with typical development and no first-degree relatives with a diagnosis of ASD or ADHD. Inclusion criteria include full-term birth (gestational age > 36 weeks). At the time of enrolment, none of these infants had a known medical or developmental condition.

Additionally, twenty-five infants with NF1 diagnosis at 14 months of age (+/- 3 weeks; Table 6.1) were also recruited (see Chapter 4.2.1 for details of recruitment procedure). Infants with an NF1 diagnosis were recruited though local and genetic centres as part of the EDEN study. All participants had their diagnosis confirmed via molecular testing of cord blood samples or clinical diagnosis based on NIH consensus criteria. Medical history and records of developmental concerns were taken during the visit. No other exclusion criteria were applied during recruitment of this population (see Table 6.1 for numeric classification of group status used in present analysis).

There were differences in the total number of EEG recordings and total number of participants per group (see Tables 6.1 and 6.2), as some infants were not able to take part in the protocol due to tiredness or becoming upset during the recording.

Table 6.1 *Numeric combinations of family history and genetic conditions in infants recruited in the present sample.*

Familial Likelihood ID	Group Name	Age in Months and Days (SD)	*n*	ASD	ADHD	NF1
1	TL	14mo 23d (20d)	27	0	0	0
2	EL-ASD	14mo 22d (16.1d)	81	1	0	0
3	EL-ASD+ADHD	14mo 26d (22.4d)	21	1	1	0
4	EL-ADHD	14mo 27d (23.8d)	30	0	1	0
5	NF1	14mo 18d (18.8d)	25	0	0	1

6.2.2 Stimuli and apparatus.

The auditory task consisted of two types of square edge click-trains (20Hz, 40Hz) and a 500ms ISI sampled at 4.1kHz. Each click-train stimulus was 500ms in duration (1.5s in total), with the inter-trial interval (ITI) jittered around 700ms (see Figure 6.1; stimuli generated by E. Jones in MatLab®). Presentation of stimuli were ordered into first or second within a single block with a 50% probability. Note that A20 was always followed by B40 and A40 always followed by B20. The sound intensity was 70dB SPL. The sounds were delivered through speakers 1-1.5 meters in front of the infant and presented for 10 minutes, or until the infant became restless.

6.2.3 Procedure.

The auditory task was administered at the end of a battery of visual EEG tasks that were identical for both STAARS and NF1 infant cohorts. Infants were seated on the parent's lap

facing the experimenter, who blew soap bubbles or engaged in 'silent play' with toys throughout the recording session to keep the infant calm and occupied. The experiment was conducted in a sound attenuated room, where the sounds were presented from two speakers, 1 metre apart, and located 1 metre in front of the infant. The infants also took part in The Mullen Scales of Early Learning (Mullen, 1995), which were administered in the standardised format; with assessments completed in the same laboratory setting by a small team of experimenters. Parents were also asked to complete a set of questionnaires at home within two weeks of each laboratory visit, which included the Infant-Toddler Sensory Profile (ITSP; Dunn & Daniels, 2002) and the Quantitative CHecklist for Autism in Toddlers (Q-CHAT; Allison et al., 2008) questionnaires that are used in later behavioural comparisons.

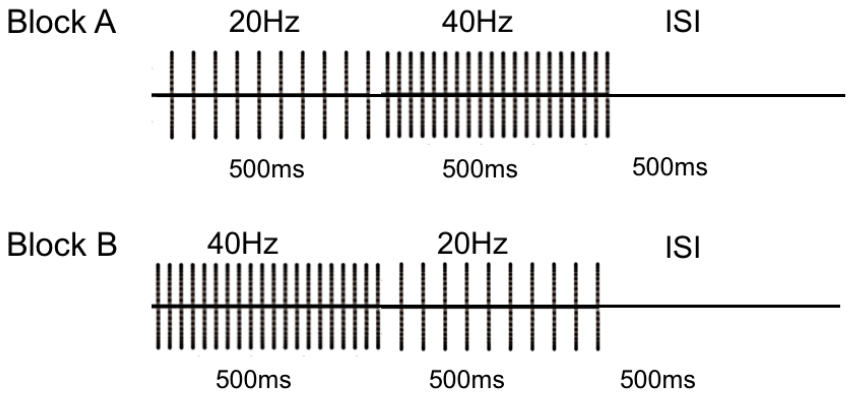


Figure 6.1 Example of trial blocks for auditory frequency modulation task. The block commences with a click train at 20Hz or 40Hz, followed by an inter-stimulus-interval (ISI) for 500ms each. Order of frequency which appears first is randomized. Block A and B are followed by the ITI, which was jittered around 700ms.

6.2.4 EEG recording and pre-processing.

Electrophysiological activity was measured as described in Chapter 4.2.4. The recording was segmented into 1000ms sections (500ms pre- and 500ms post-stimulus

presentation). Bad channels in each segment were marked by automatic artefact detection and visual inspection in NetStation (Version 4.5.6). All epochs exceeding 150μV at any electrode were excluded through automatic artefact detection. The segments with pronounced artefacts, i.e. gross motor movement, eye blinks, or more than 25 bad channels, were rejected from analysis through hand editing (116 clean datasets remained; see Table 6.2 for details). At least 20% of trials had to be retained in each category to qualify the dataset to be included in the group analysis. For the remaining trials, channels with a noisy signal were interpolated from neighbouring channels with a clean signal using spline interpolation. Data was baseline corrected between 100-0ms before the onset of stimulus. Then, the epochs were referenced based on the average reference of electrodes from the whole scalp and individually averaged across individuals and conditions. Meta data was then exported into MatLab for time-frequency analysis. Due to the jitter introduced between stimuli onset, adjustments had to be carried out during this stage to correct the timing onset of each individual stimulus based on regression from the start of the experiment based on in-house scripts (see Chapter 2.5.2.1).

6.2.5 Time-frequency analysis.

The pipeline for analysis of present data follows a protocol analogous to analysis of EEG/MEG data in the time-frequency domain by Popov, Oostenveld and Schoffelen (2018), who described several ways to analyse the ASSR in adult populations using analysis scripts made available in Fieldtrip (*ASSR_timefreqdomain.m*; https://data.donders.ru.nl/). Note that this analysis returns power (amplitude squared) values, i.e. ERSP, which are in contrast to the wavelet analysis described in Chapter 5. Time frequency analysis with a Hanning window was carried out with respect to a time window that varies with frequency[30] (i.e. time window gets

shorter with increasing frequency; similar to wavelet analysis described in Chapter 2.4.8 and Chapter 5). The number of cycles per time window was 3, increasing by 0.5 with increase in frequency applied over 15-50Hz. Time interval of the analysis was -100 to 500ms in steps of 50ms (this was sufficient resolution without requiring too much computational time). A single-trial baseline procedure was then used from -300ms to 0ms, which is more suitable than applying baseline on an average for noisy data. Next, grand averaged frequency domain activity was computed and visualised -400 to 400ms post stimulus onset; this was used to determine the frequency bands of interest accounting for smearing around the target frequency band (see Chapter 6.2.6).

[30] Several spectral decomposition methods are available

(see http://www.fieldtriptoolbox.org/tutorial/timefrequencyanalysis).

Table 6.2 *Data retention rates per group for the ASSR task.*

Familial Likelihood ID	Group Name (*n*)	*N* Participants Retailed / Total EEG Recordings	Total Trials (Clean/Total Administered)	Condition (Mean, SD)		
				20Hz	40Hz	ISI
1	TL (27)	14 / 16	573.26 (896.6)	91.83 (31)	92.1 (30.1)	298.8 (72.8)
2	EL-ASD (81)	48 / 61	505.6 (768)	83.75 (30.5)	85.66 (28.7)	293.1 (31.2)
3	EL-ASD+ADHD (21)	13 / 16	460.9 (900)	76.07 (20.5)	77.73 (19.7)	300 (0)
4	EL-ADHD (30)	16 / 22	493.58 (800.2)	81.9 (21.4)	80.7 (20.8)	294.1 (23.3)
5	NF1 (25)	12 / 19	355.2 (837.5)	58.09 (21.14)	58.63 (19.5)	300 (0)

Note. The number of trials is averaged for first and second presentation order (i.e. 20Hz = A20Hz and B20Hz). A univariate ANOVA showed significant group differences in the number of clean trials retained for analysis for 20Hz ($F(4,95)=2.97$, $p=.023$, $\eta_p^2=.116$), 40Hz ($F(4,95)=2.97$, $p=.023$, $\eta_p^2=.116$), and ISI ($F(4,95)=2.97$, $p=.023$, $\eta_p^2=.116$) conditions. There were no differences found in the number of trials administered ($p=.25$, $\eta_p^2=.051$). Follow up analyses showed significantly lower number of trials retained for analysis in the NF1 group. Differences between total sample size and total number of recordings are discussed above. Number of participants retained was influenced by number of trials >30% and overall data quality for the individual dataset.

6.2.6 Statistical analyses.

The power values for each individual were extracted in four temporal windows (i.e. 50-100ms, 100-200ms, 200-300ms, 300-390ms[31]) and exported to SPSS for statistical comparison. The temporal windows were selected based on averages of the data due to lack of previous literature supporting particular windows of the ASSR. For each modulation condition, the frequency band of interest was centred around a 10Hz window centred on the modulation frequency (+/-5Hz). For the 20Hz ASSR, power was defined as total power averaged over 15-25Hz; and 40Hz ASSR, power was defined as total power averaged over 36-46Hz. As described in Chapter 6.2.1 and Table 6.1, participants were given a likelihood factor (ASD-L, ADHD-L) depending on family history. The likelihood was computed in this way so that it would be possible to look at the individual influence as well as the interaction of the disorders as well as isolate additive/protective factors. If there were indicated interactions between likelihood groups, the data was split by group for a more traditional analysis approach (EL-ASD, EL-ADHD, EL-ASD+ADHD, TL). An additional analysis was carried out between the TL and the NF1 group, who have increased likelihood of both conditions.

Due to the exploratory nature of this task, statistical analyses to identify the ASSR were split into three stages. Firstly, the temporal and spatial windows in which the ASSR was strongest were determined (strength of power response for all experimental conditions across all groups, with separate effects of Region and Laterality). Then, the driving response was assessed, i.e. whether there were frequency-specific differences in response to 20Hz and 40Hz stimulation. Within the same model, the effects of order of stimuli were examined as a possible

[31] End of window based on the wavelet.

alternative to the ASSR by comparing power between the order of the click trains (Freedman et al., 1987; Orekhova et al., 2008). The ISI condition was excluded from present analysis as it acted as a baseline for the first presentation of the click train (A20 or A40), and can therefore not be fully distinct from the modulation conditions.

Repeated measures ANOVAs were carried out to look at these effects (see Chapter 2.5.2.3 and Figure 2.5 for electrodes chosen). Total number of 'clean' trials and age (in days) were entered as co-variates to each model. Greenhouse-Geisser corrections were applied where appropriate. Effect of ASD/ADHD likelihood and were carried out by replicating the significant models (Chapter 6.2.1). Interaction with ASD and ADHD familial likelihood were examined to establish whether there are additive/protective effects between group status and the ASSR (Chapter 6.1.4). In an additional model, responses from NF1 group were compared to the TL infants to look at possible effects of the genetic syndrome on ASSR.

Lastly, associations with behavioural phenotype were assessed by correlating the power change sensitive to group differences with scores on the Expressive and Receptive Language subscales on the Mullen (Mullen, 1995), total score on the Infant-Toddler Sensory Profile (ITSP; Dunn & Daniels (2002)) and total score on the Quantitative Checklist of Autism in Toddlers assessment (Q-CHAT; Allison et al. (2008)). The data was derived from parent and observer ratings during the 14-month visit. The model attempted to isolate dimensional relationships between electrophysiology and behaviour by comparing associations irrespective of familial or genetic history of the individual infant.

6.3 Results

6.3.1 Identifying temporal and spatial ROI of the ASSR.

Firstly, the strength of ASSR response was compared across different spatial and temporal regions of interest. This was done in order to identify a region which was most

sensitive to the driving response across all infant groups. It should be noted that the majority of the total sample are from the EL-ASD group and the strategy of choosing an ROI from the total sample meant that the overall response was most reflective of the pattern of that group. This limitation was further addressed in the Discussion. Two repeated-measures ANCOVAs were run with Frequency Band (15-25Hz vs. 36-46Hz), Condition (40HZ vs. 20Hz), Temporal window (50-100ms vs. 100-200ms vs. 200-300ms vs. 300-390ms), Region (Frontal vs. Central vs. Temporal) and Laterality (Right vs. Left) as within-subjects variables, controlling for effects of Age (in days) and Trial number.

6.3.1.1 Temporal and Spatial ROI for power in the beta band (15-25Hz).

For the first repeated measures ANOVAs, activity in the beta band was investigated in response to the 20Hz and 40Hz stimulation frequencies. The model revealed a significant Temporal Window x Condition interaction ($F(3,252)=2.67$, $p=.048$, $\eta_p^2=.031$). There was also an overall main effect of Time Window ($F(3,82)=16.9$, $p<.001$, $\eta_p^2=.38$). As can be seen in Figure 6.2A, the beta-band responses increased in strength over time, with significantly higher responses visible over 200-300 and 300-390ms time windows. Bonferroni corrected pairwise comparisons showed higher responses than 50-100ms and 100-200ms time windows (all ps<.003), but not between 200-300 and 300-90 (*Mean diff.*=.044, $p=.070$, *CI*[-.002 .090]), where highest power of response was detected irrespective of Condition. There was also a significant main effect of Region ($F(2,83)=5.04$, $p=.009$, $\eta_p^2=.108$), with pairwise comparisons showing higher power in Central than Parietal (*Mean diff.*=.107, $p=.009$, *CI*[.021 .192]) but not the Frontal region (*Mean diff.*=.075, $p=.116$, *CI*[-.012 .162]). There were no significant main effects of Laterality or Condition or other interactions within the beta frequency band responses.

6.3.1.2 Temporal and Spatial ROI for power in the gamma band (36-46Hz).

Next, responses over the gamma band (36-46Hz) were examined over time and cortical region. There was a significant Time Window x Region interaction ($F(4.2, 362)=2.42$, $p=.042$, $\eta_p^2=.028$). Pairwise comparisons showed significantly higher power values over 200-300ms in the Central than Temporal (*Mean diff.*=.126, $p=.016$, *CI*[.018 .233]) but not Frontal regions (*Mean diff.*=-.027, $p=.1$, *CI*[-.119 .015]). Additionally, there were significantly higher power over 300-390ms in the Central than Frontal (*Mean diff.*=.135, $p<.001$, *CI*[.055 .215]) or Temporal (*Mean diff.*=.165, $p=.005$, *CI*[.041 .289]) regions. As can be seen in Figure 6.2B, the Central region has the highest responses over the late portion of the waveform. There were no significant main effects of Condition or Laterality, nor other significant main effects.

Based on the analysis, further models were constrained to Power over 200-390ms within the Central electrodes. As defined by Rojas and colleagues (2011), responses over 50-100ms are likely to capture the 'transient' gamma activation, which is not investigated in the present task. On the other hand, beta and gamma activity appears to increase from 200ms onwards, as shown in Figure 6.2A and B. In addition, the ASSR has been studies in central electrodes in the literature (Popov et al., 2018; Poulsen et al., 2009; Puvvada et al., 2018).

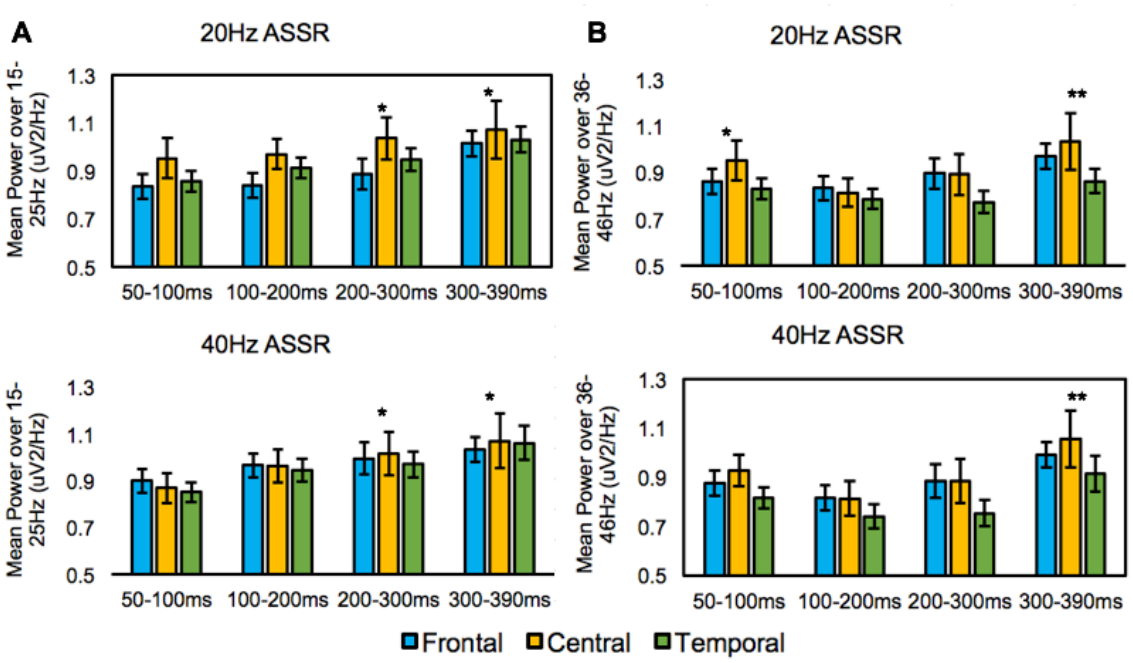


Figure 6.2 Bar plots of mean power for 20Hz (top row) and 40Hz (bottom row) stimulus repetition rates visualized across three chosen ROIs across the scalp and averaged over laterality. Power is visualised in columns over **(A)** beta and **(B)** gamma frequency bands. Black rectangles represent where maximal response was expected following the stimulus (e.g. higher 15-25Hz power in response to 20Hz condition). It can be seen that higher power was reported 200-300ms and 300-390ms, mainly over central electrodes. Note. **p<.001, *p<.05. Error bars represented 95% CI.

6.3.2 Frequency-specific differences: can we drive beta and gamma-band responses in infants?

The next model looked at whether the click train stimuli were able to elicit a driving response over 200-390ms in the central ROI that was frequency-specific to the stimulus (e.g. an increase in 40Hz power in response to 40Hz stimulation). A series of repeated measures ANOVAs were carried out for the two Frequency Band conditions separately (15-25Hz and. 36-46Hz) with Order (A vs. B) and Condition (20Hz vs. 40Hz) as within-subjects and ASD-L (0 vs. 1), ADHD-L (0 vs. 1) as between-subjects variables. Frequency-specific effects were defined as significantly higher power within the beta/gamma bands following respective ASSR condition. A second model was run comparing frequency-specific effects in the TL vs. NF1

group. Age (in days) and Trial number were entered as covariates. Group ERSP plots per frequency modulation condition have been visualised in Figure 6.3.

6.3.2.1 Examining frequency specificity of beta-band activity (15Hz-25Hz).

The first model examined driving of the beta band responses to the 20Hz and 40Hz stimulus repetition rate across familial ASD/ADHD likelihood groups. There were no significant effects of Order of presentation ($F(1,72)=.176$, $p=.676$, $\eta_p^2=.002$) nor Condition ($F(1,72)=.337$, $p=.56$, $\eta_p^2=.005$), which suggested that there was no entrainment of beta frequency responses to either 20Hz or 40Hz stimulation rate. Additionally, there were no significant effects of ASD_L ($F(1,72)=.628$, $p=.431$, $\eta_p^2=.009$) or ADHD_L ($F(1,72)=.079$, $p=.779$, $\eta_p^2=.001$). There were no significant interactions between ASD and ADHD likelihood on beta-band activity ($F(1,72)=2.25$, $p=.138$, $\eta_p^2=.030$). In an additional model looking at NF1 vs. TL groups only, which did not find effects of Order ($F(1,21)=.245$, $p=.626$, $\eta_p^2=.012$), Condition ($F(1,21)=.003$, $p=.960$, $\eta_p^2=.001$) or NF1_L $F(1,21)=.566$, $p=.46$, $\eta_p^2=.026$); which suggested there was no difference in beta-band power in response to click train stimuli in the NF1 group.

6.3.2.2 Examining frequency specificity of gamma-band activity (36Hz-46Hz).

Next, driving of gamma-band responses were examined. The model did not reveal a significant effect of Order ($F(1,72)=.131$, $p=.719$, $\eta_p^2=.002$) or Condition ($F(1,72)=.227$, $p=.635$, $\eta_p^2=.003$). In addition, there were no between-subject effects of ASD_L ($F(1,72)=.015$, $p=.904$, $\eta_p^2=.001$) or ADHD_L ($F(1,72)=.001$, $p=.982$, $\eta_p^2=.001$) on gamma-band power, which suggested there were no robust entrainment of gamma to 20Hz or 40Hz stimulation and no significant differences between infants across different familial likelihoods of developmental conditions. In an additional model looking at NF1 vs. TL groups only, there

were no significant effects of Order $F(1,21)=1.98$, $p=.174$, $\eta_p^2 =.086$), Condition ($F(1,21)=.299$, $p=.679$, $\eta_p^2 =.011$) or NF1_L $F(1,21)=.164$, $p=.69$, $\eta_p^2 =.008$).

It should be noted that there was an effect of Order of presentation was not significant for either beta or gamma-band power for any groups in the analysis, which contradicted the original hypothesis that there may be habituation/gating effects based on the order of click trains. This is visualised in Figure 6.4.

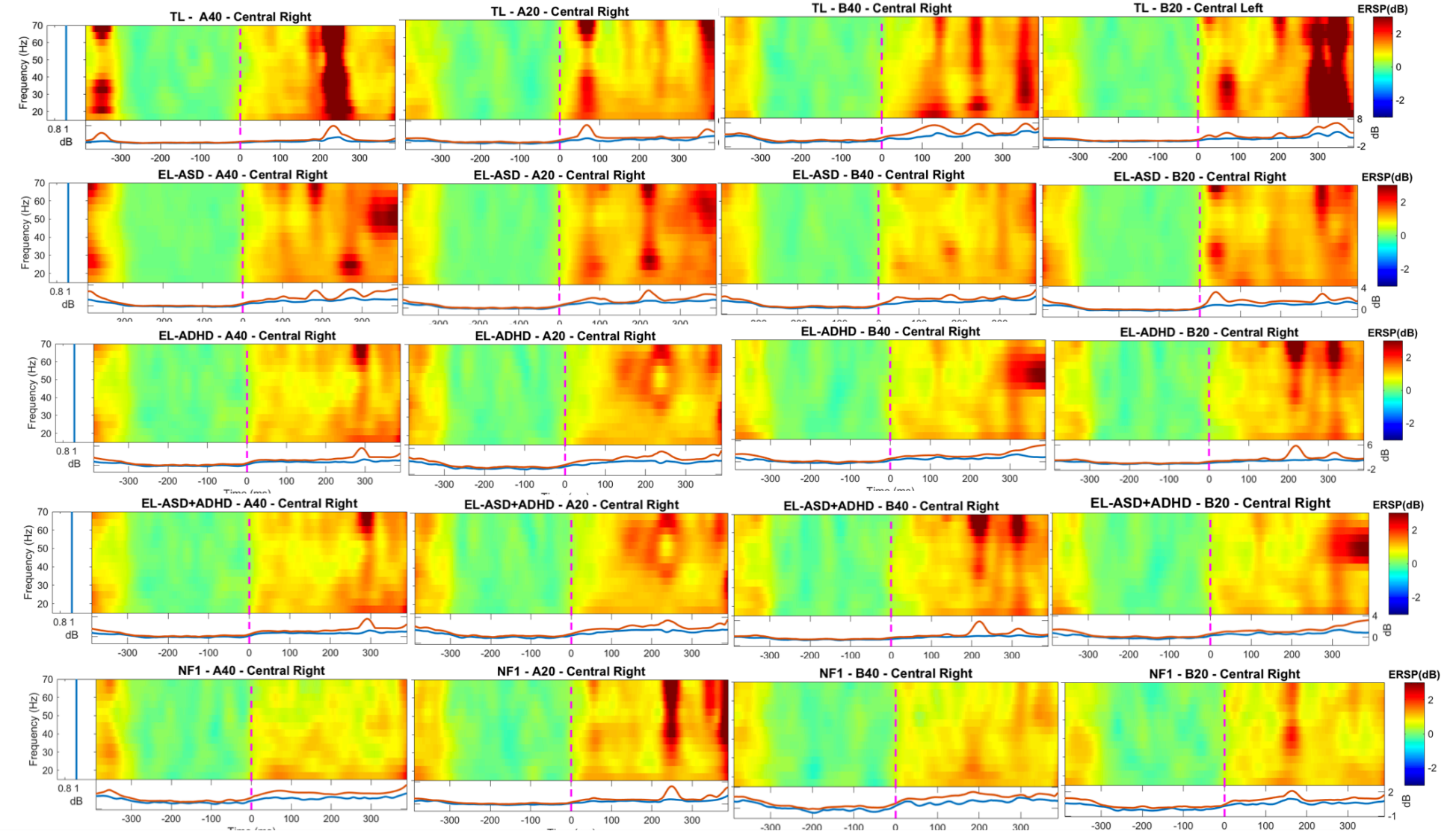


Figure 6.3 ERSP plots for all groups in the experiment visualised in the Central ROI; Right hemisphere is shown. On a group level, there were no significant effects of Condition on frequency band of interest (15-25Hz and 36-46Hz). Higher frequencies (50Hz+) were not analysed.

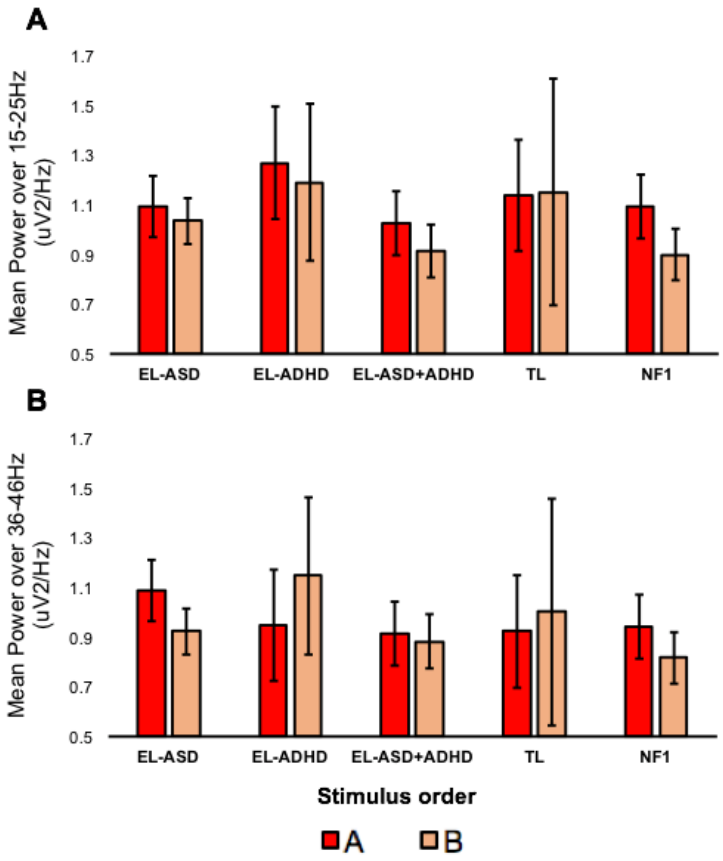


Figure 6.4 Bar plots to show effects of stimulus order of presentation across infant groups. Mean power values over **(A)** 15-25 or beta band and **(B)** 36-46Hz or gamma band averaged over presentation rate of the stimuli (i.e. 20Hz ASSR and 40Hz ASSR) over central ROI. Note that separate comparisons were run between TL infants with added ASD or ADHD likelihood, as well as a model between TL and NF1 group. As can be seen, there were no robust differences between groups and no significant effects of the order of stimulus. Note. Error bars represented 95% CI.

6.3.3 Behavioural comparisons.

Contrary to the predictions set out at the start of the experiment, there were no frequency specific responses to 20Hz or 40Hz stimulus presentation rates, nor clear differences between groups. Due to this, the behavioural comparisons were not conducted, as the response

in question was not specific to individual group status and was therefore unlikely to yield meaningful results.

6.4 Discussion

The results of the frequency modulation task revealed that there were no frequency specific responses in beta or gamma-band power to 20Hz or 40Hz click trains in 14-month-old infants. The following discussion evaluates the results of the task based on the aims, specifically the feasibility of using ASSR paradigms in infants as well as the specificity of the response to familial or monogenic ASD likelihood, prior to onset of behavioural symptoms.

6.4.1 Feasibility study: can 40Hz ASSR be detected in awake infants using EEG?

Contrary to predictions, no frequency sensitivity was reported in infants towards either 20Hz or 40Hz stimulus repetition rate. The findings contracted previous literature, in which large gamma band activation has been reported in newborns and three-year olds (Oliveira et al., 2014), as well as the wealth of audiology and psychological studies of the 40Hz ASSR with adults (Azzena et al., 1995; Boettcher, Madhotra, Poth, & Mills, 2002; Boettcher, Poth, Mills, & Dubno, 2001; Ross, Herdman, & Pantev, 2005; Stapells, Makeig, & Galambos, 1987; Wilding, McKay, Baker, Picton, & Kluk, 2011). It should be noted that the present study was the first to look at ASSR in awake infants, and therefore the results have been informative for future research into the field. Especially because the presence of 40Hz ASSR has been a widely-disputed topic in infant and child literature. Present findings feed into the school of thought that mechanisms of temporal processing are immature at 14 months, an age where the initial specialisation of the auditory cortex towards speech and language sounds has taken place (Edgar et al., 2016; Tlumak et al., 2012). It should be noted that maturation of activity within the gamma range is not specific to the auditory cortex and visual gamma activity in response

to movement been reported to increase in synchrony between childhood and adolescence in the motor cortex (Gaetz et al., 2010).

There has been wide speculation about the late development of the ASSR that continues into early adulthood. Poulsen suggested that immature ASSR in children reflected the continuous specialisation of the auditory cortex towards processing of rapid temporal information (Ehlers et al., 2014; Poulsen et al., 2009). Poulsen and colleagues (2009) used their findings of weaker ASSR in the left than the right hemisphere to reflect the more slowly developing left hemisphere, which is somewhat supported by present observations. Based on current findings, there was some evidence of stronger ASSR in the right than left hemisphere, although the effects did not survive statistical correction. One of the possible explanations to elevated responses in the right hemisphere was due to the child's position during the experiment as speakers were more likely to be closer to the left ear as the infant looked toward the experimenter.

The limitations of the present study's design have to be considered. The choice of stimuli was based on several previous studies (Rojas et al., 2011; Ross et al., 2000; Tlumak et al., 2012; Wilson et al., 2007). However, the results of those studies were inconsistent and used different baseline measures and signal processing techniques, which has meant that the literature is not easily compared. Additionally, there has been reported differences between ASSR in relation to ISI (Bernhard Ross et al., 2002). The relationship was not explored in the present investigation as the stimulus gap was acting as a baseline for the first but not the second train click and would have therefore skewed the differences across order of stimulus presentation. One of the issues with investigating gamma-band power is the possible low-amplitude muscle artefact contamination, as discussed in Chapter 5. However, muscle artefact is less likely to affect present findings because (1) the artefact primarily occurs in non-phase locked/induced activity i.e. resting state power and (2) is prevalent to the visual rather than

auditory EEG studies (Gross et al., 2013; Kampis et al., 2016; Schwartzman & Kranczioch, 2011).

As mentioned previously, the infants were awake during the task, and therefore had to be engaged by researchers in order to maintain compliance. Typically, the researcher would blow bubbles or occupy the infant in silent play with toys; although noise levels were difficult to control once the infant was playing. It was therefore difficult to estimate whether the volume of the stimulus in the booth was adequate/equal to both ears to produce a strong ASSR. The design setup differed to other ASSR studies, where the auditory stimuli are delivered directly into the ear via a headphone (Maurizi et al., 1990; Popov et al., 2018), which would produce maximal responses. This is somewhat reflected in the effect sizes of the present analyses. Significant main effects and interactions in the results above range between and .03-.04 partial eta squared, which are considered small (Cohen, 2013; Lakens, 2013). The effect of region and time window in the beta and gamma bands was .1-.38, which suggested that there was considerable change over time post stimulus onset. These effect sizes suggest that there was sufficient power to detect 40-Hz ASSR group differences. Non-significant results had effect sizes between .001 and .005, which suggests that there were no potential trends that could be significant under alternative analysis methods (i.e. Bayesian modelling). Present results closely resembled those reported by Edgar and colleagues (2016), who did not report 40Hz ASSR in the majority of individuals, and found higher effect size for hemisphere rather than group comparisons, and concluded that 40Hz ASSR is weak/ not developed until early adulthood (Edgar et al., 2016). In addition, several previous investigations reported stronger ASSR to attended than non-attended stimuli, which could also be used to explain present findings (Lazzouni, Ross, Voss, & Lepore, 2010; Ross, Picton, Herdman, & Pantev, 2004). Nonetheless, the present design was optimised for the young participant group. The single headphone was not used for comfort of the infants and ease of administration of the task.

Overall, the findings showed a lack of frequency specificity within beta and gamma bands to 20Hz and 40Hz stimulus repetition rates in a group of awake infants. It should be noted that there was an overall increase in power towards the end of the measurement window that was not frequency specific (300+ms, Figure 6.3). Previous mice research found that an increase within the high beta and gamma frequency ranges indicated cortical binding and increased in cognitive performance (Marrosu et al., 2006), which suggested that the overall mechanism may be used as a developmental tool for encoding of rapid temporal processing information. Additionally, 20Hz stimulus repetition rate has been reported to generate ASSR within the beta and gamma frequency band due to harmonics (Oda et al., 2012; Xiaodan Tan et al., 2017), while the 40Hz repetition rate has been reported to generate only gamma-band activity. Research from adults with SCZ had found that ASSR reflected the efficiency of GABAergic inhibitory interneuronal activity, which regulated the timing of pyramidal neurons in II/III cortical layers (Brenner et al., 2009; Cunningham et al., 2004; Gonzalez-Burgos & Lewis, 2008). As no stimulus entrainment was found in TL or EL groups, it could be argued that the links between gamma band activity and the E/I balance in the cortex are not yet established at 14 months.

6.4.2 ASSR and the effect of ASD/ADHD likelihood.

Several studies reported atypical 40Hz ASSR in individuals with ASD, ADHD as well as neurodevelopmental or genetic conditions which suggested there may be a common pathway that could be observed from early development. However, no group differences were observed, which could be explained by two reasons: (1) the diagnostic criteria in the elevated likelihood groups were based on family history, of which 20% of infants are predicted to go onto receive a diagnosis of ASD and up to 26-45% ADHD (Hidalgo-López et al., 2019; Ozonoff et al., 2011) and, as argued previously, (2) it was possible that due to protracted maturation of the NMDA pathways and protracted maturation of inhibitory interneurons, the infants were too

young for a measurable ASSR to be observed (Carlén et al., 2012; Edgar et al., 2016; Presacco et al., 2010; X.-J. Wang, 2010). However, previous literature has suggested weak function-structure relationship between the ASSR and grey matter changes in children and adolescents and has warranted further exploration through longitudinal human or animal work (Edgar et al., 2014, 2016).

Furthermore, previous studies have reported atypical 40Hz ASSR in children with ASD that were more cognitively impaired (Edgar et al., 2016; Wilson et al., 2007). Wilson and colleagues (2007) studied children with mean IQ of 92 and found atypical ASSR, but another study by Edgar and colleagues (2016) with a mean IQ of 107 did not report similar differences. There were no significant associations between gamma or beta power and scores on the Mullen subscales, and further work would be required to assess the early ASSR responses of infants with later low-functioning ASD or intellectual disabilities retrospectively.

A possible drawback of the design used in the present study was the high number of infants in the EL-ASD group relative to other groups in the analysis (Table 6.1), which had arguably skewed the identification of temporal/spatial ROIs where the response was strongest. One possible way to avoid this was to identify the ASSR in the typically developing control group only (i.e. TL) and restrict the analyses to the specific temporal and spatial region for other groups, as described in Chapter 5. However, due to the exploratory nature of the task and lack of previous literature on the ASSR in young infants and children, no participant groups were excluded from analysis. Additionally, a direct comparison between TL and NF1 or TL and EL groups during follow-up tests did not reveal group differences in entrainment.

Overall, it can be argued that there were no differences within the ASSR in infants with familial likelihood of ASD/ADHD. Further longitudinal research is needed to look at age-dependent change in ASSR in order to develop effective treatment protocols.

6.4.3 Differences in ASSR in infants with a diagnosis of NF1, what can we learn?

There were no significant differences gamma or beta responses to frequency modulation between infants with NF1 and those with no family history of neurodevelopmental or genetic conditions. The finding is in contrast to findings of atypical ASSR in children and adults with genetic conditions (Khaleghi et al., 2019; Larsen et al., 2018; Rotschafer & Razak, 2013), which suggested that there may be maturational factors affecting the development of the driving response beyond infancy. However, the high acquisition and retention rates from the study within the NF1 population suggest that passive auditory paradigms are well tolerated by this population.

Ultimately, the frequency modulation task failed to elicit the expected auditory steady-state response in infants at 14 months of age, irrespective of familial or monogenic likelihood of developmental conditions. It offers possible insight into the protracted maturation of inhibitory interneurons and the Excitation/Inhibition balance overall, offering larger potential windows in which interventions can be delivered than previously believed. Further work is needed to understand how the response may change across early-late childhood in order to establish age-related differences across developmental trajectories.

Chapter 7. General Discussion

This chapter summarises the findings from eye tracking and EEG tasks described in Chapters 3-7 and considered how results of the investigations relate to the wider literature on experience-dependent specialisation and emergence of communication skills in preverbal infants. First, I highlight the key findings from the longitudinal study, GABBLES (Chapters 3-4), and what we were able to learn from a combination of multiple methodologies about the precursors of verbal communication in typical development, as well as sensitivity of the selected metrics to native and non-native languages and individual language experience. Then, I consider results of the three EEG tasks (Chapters 4-6) and how these findings related to literature on emergence of processing of verbal and non-verbal information in the auditory cortex in individuals with familial or monogenic likelihood of ASD. Finally, I relate these findings to the driving hypotheses behind this work and put forward some practical guidance for clinicians and researchers working with rare genetic disorder populations such as NF1. Experimental findings of this thesis are discussed in relation to the aims set out in Chapter 1:

"Based on the current evidence, the main questions that will be addressed by this work are:

4) It is possible to capture early specialisation towards the native language in typically developing infants using novel eye tracking paradigms?

- *Are infant-driven and naturalistic eye tracking experiments equally able to capture specialisation, i.e. increase in perceptual narrowing and increasing preference towards the native language with age (Chapter 3).*
- *Can relationships be established with EEG-based markers of auditory processing and the behavioural phenotype? (Chapter 4).*

5) Can putative EEG-based markers of auditory cortex specialisation be established and are they predictive of later language outcomes in toddlerhood?

- *What are the age-related changes in early auditory processing and can I establish relationships with parent and observer report of early child development? (Chapters 4-6).*
- *Do infants display different cortical responses to basic auditory stimuli depending on their likelihood of neurodevelopmental conditions such as Autism Spectrum Disorder (Chapters 5-6) or ADHD (Chapter 6)?*

6) And finally, what are the differences in early communication in infants with the rare genetic disorder Neurofibromatosis Type 1?

- *Are infants with a diagnosis of NF1 showing age-related differences in speech processing relative to neurotypical infants?*
- *Are there group differences between infants with NF1 and those with idiopathic ASD/ADHD? Are established EEG measures of specialisation sensitive in capturing similarities/differences between these populations? (Chapters 4 and 6).”*

7.1 Summary of Key Findings

The main aim of this work as set out in the General Introduction, has been to explore early markers of communication development in preverbal infants – using behavioural and electrophysiological methodologies. Findings of this thesis have provided insight into the aims set out at the start of the investigation, namely that reliable indices of specialisation of communication could not be established through eye tracking alone, and that EEG-based markers, i.e. auditory habituation appeared most sensitive in predicting later communication abilities as well as developmental outcome across several conditions. In addition to investigating experience-dependent specialisation longitudinally in a neurotypical population, the effects of familial or monogenic likelihood of ASD were also examined. Below, I evaluate what the early differences/commonalities across these groups suggest about early development.

Lastly, I consider age-related changes in functional brain specialisation and suggest avenues for future research.

7.1.1 Measuring functional specialisation using novel eye tracking paradigms.

I begin this discussion by considering the markers of experience-based specialisation observed in typically developing infants using eye tracking and EEG-based measures. Three eye tracking tasks were administered as part of a longer task battery that were specifically designed to address aspects of emerging communicative behaviour. The abilities measured included increased preference towards the native versus non-native language (Active Seeking, ET Task 1), audio-visual matching between language and mouth shape of the speaker (Audio-visual Matching, ET Task 2) as well as attentional shift between eyes and mouth (Selective Attention, ET Task 3). All three tasks were adapted from existing paradigms in order to obtain a more 'spontaneous' or naturalistic responses than reported in the previous literature; including gaze-contingency in Task 1, as well as absence of training periods or 'baselines' used in analogous versions of Task 2 and 3. Although there were some clear effects of age on reaction time and pupil dilation, the evidence to support experience-based specialisation towards the native language was limited. Specifically, task performance did not show internal consistency across age points, and no associations were observed between selected metrics of looking behaviour and parent/observer ratings of language ability. As the results did not consistently meet pre-defined criteria of a reliable index of experience-dependent specialisation (see Chapter 3, Table 3.5), it was concluded that eye tracking may not be sensitive enough on its own to look at predictors of early developmental atypicalities within an infant sibling design.

The findings showed clear inconsistencies with previous literature. Several studies have argued that neonates and infants demonstrate a clear preference to speech and that this preference narrows towards the native language over the first year of life (Bosch & Sebastián-Gallés, 1997; Elsabbagh, Hohenberger, et al., 2013; Moon et al., 1993). Others reported that

infants showed dynamic change in selective attention and audio-visual matching that are indicative of underlying brain specialisation (Barenholtz et al., 2016; Lewkowicz & Hansen-Tift, 2012). Somewhat conflicting evidence to these claims has been reported in a series of eye tracking experiments in the present thesis (which are considered in more detail in Chapter 3.15). The implication of findings is that looking time measures within the particular set of tasks did not provide a strong index of functional brain development. Specifically, the small effect sizes present in adapted audio-visual integration and selective attention tasks may suggest that they were not sensitive enough to record substantial developmental changes. The conclusion is further supported by previous investigation by Keen (2003), who reported that task differences (e.g. adding an active choice element) can affect the likelihood of a desired effect. As a result, the findings highlight the importance of methodology itself during eye tracking paradigms when studying early development. All three tasks differ to present literature in that they were designed to capture spontaneous use of communication abilities based on a naturalistic interaction, rather than rigorous experimental manipulation (Johnson & Zamuner, 2010; Lewkowicz & Hansen-Tift, 2012; Sebastián-Gallés, Albareda-Castellot, Weikum, & Werker, 2012). The lack of robust age/stimulus language effects on infant perception is likely to suggest that there may be a general overemphasis of adult-like communication abilities in young infants (Keen, 2003). Furthermore, many previous studies looked at presence of a particular ability only in one age group. An important drawback of this design is that it is not possible to understand whether the results reflect the same mechanisms in infants as they do in adults. This is particularly evident in the study by Lewkowicz & Hansen-Tift (2012), where 4-month-old infants and adults looked more towards the eyes of the speaker, while there was a U-shaped curve in looking towards the mouth are between 6 and 12 months of age. Observing only the youngest and oldest participant groups in this task would have led to the erroneous conclusion that eyes are the main area for information sampling. Therefore, the tasks described

in this thesis examined infant looking behaviour at several time-points over the first years of life. On the other hand, there was a lack of internal consistency on task performance across all three eye tracking tasks, which warrants further investigation. It is also important to reiterate that the moderate sample size of the subgroups identified based on language experience (i.e. the ALE group) may have impacted the overall strength of experimental effects. This is reflected in the variability of effect sizes reported, ranging from small to medium for main effects and interactions observed.

Nonetheless, two eye tracking metrics that showed robust age and stimulus language effects were selected to be compared against behavioural and electrophysiological data. They included pupil dilation changes and looking time towards native and non-native infant-directed phrases in Task 1, Chapter 4. It was found that pupil dilation was positively associated with the degree of auditory habituation in the Auditory Trains EEG task – i.e. infants who were better able to habituate to stimulus repetition also showed higher pupil dilation in response to a language stimulus at 5 and 10 months of age. Although initial aims of this work did not set out the direction of the relationship between eye-tracking and EEG indices, it was logical to observe that an increase in habituation ability to vowel sounds would be related to greater arousal levels to language stimuli. A common interpretation of increased pupil size in infancy, beyond a basic response to changes in luminance, is the detection of novelty (Eckstein et al., 2017; Hepach & Westermann, 2016), and therefore would inversely reflect the increase in sensory discrimination ability indexed by neural habituation. The association between pupil size and neural activity has been further reported in bilingual children and adults (Kuipers & Thierry, 2011, 2013). Both studies showed that a positive association between pupil size and N400 amplitude was related to better semantic integration in bilinguals but not monolinguals, providing a neural basic for cognitive advantage in bilinguals. The association between ERP and pupil size have been corroborated by a mouse model in an oddball paradigm (Takahashi et

al., 2015). One of the possible ways of examining the relationship directly is through combined EEG and eye tracking in infants (Kulke et al., 2017, 2017), although pupil dilation has not been studied directly in these studies.

However, there are significant methodological considerations when interpreting pupil diameter, specifically due to the influence of luminance. In present studies, luminance levels were kept consistent within each task respectively using background colour. On the other hand, levels of individual arousal were not controlled, which complicated the interpretation of present findings (Wang et al., 2018). Future research would benefit from simultaneous movement and heart-rate recordings, where arousal levels could then be used to baseline visual behaviour. There is further need to investigate the protracted development of pupillary activity in populations with elevated likelihood of developmental conditions, as early atypicalities in habituation responses reported in infants with NF1 (Chapter 4) and later ASD (Chapter 5) suggest there may be delayed/absent change in pupil dilation to language stimuli with age.

Data from the auditory trains task described in Chapter 4 further revealed age-dependent change within the infants' habituation response; and it was argued that EEG-based markers may be more sensitive than eye tracking measures alone in reflecting brain specialisation in young infants, as argued below.

7.1.2 EEG-based metrics of specialisation predict behavioural phenotype.

Next, I summarise the results of three EEG tasks that were carried out in order to identify neural markers of specialisation in both typical and atypical development. Two EEG tasks which partly addressed mechanisms of habituation across different infant populations suggested that infants 5-8 months of age with later diagnosis of idiopathic ASD or those with NF1 showed reduced or absent neural repetition suppression (Chapters 4 and 5). Findings from a more traditional version of an auditory oddball task using pure tones in Chapter 5 showed that infants with later ASD showed increased gamma activation following repetition relative

to infants with familial history of the condition who were typically developing. These findings suggested that atypical habituation may be a predictor of later developmental outcome, although there were no differences observed in the ERP responses (Guiraud et al., 2011). Further, individuals with later ASD had higher overall inter-trial coherence or phase locking relative to typically developing peers, which was consistent with previous literature (Ethridge et al., 2016; Milne, 2011; Rojas & Wilson, 2014). A combined index of cortical reactivity composed from gamma and ITC was further related to severity of social and language ability at 3 years, which suggested that early brain responses to repetition may be a useful predictor of later behavioural phenotype. The conclusion supports theories from the literature on the downstream effects of Excitation/Inhibition imbalance on later information processing and social communication difficulties (Canitano & Pallagrosi, 2017; Lee et al., 2016; Yizhar et al., 2011) and offers a non-invasive way of measuring E/I atypicalities in awake infants.

These findings further added to the importance of auditory habituation as a neural basis of behaviour. Habituation is a fundamental brain mechanism that extends over processing of stimuli across different modalities and constitutes a basic form of learning from as early as the last trimester of pregnancy (Muenssinger, Matuz, et al., 2013; Sheridan et al., 2008). The mechanism has been particularly important in study of infants and children, due to its potential to detect atypicalities in language processing (Benasich & Tallal, 1996; Kaplan, Goldstein, Huckeby, & Cooper, 1995). Overall, evidence presented in this thesis suggests that habituation is detectable through ERP and gamma-band responses in typically developing infants. Presence of NF1 or later ASD diagnosis resulted in a reduced/absent habituation response as well as poorer language outcomes.

Lack of group differences in response to auditory deviants may suggest that infants with later ASD were equally able to detect change, which provides further support for the specificity of auditory habituation as a marker of later atypical social and language function.

However, the findings are in contrast to previous investigations of auditory deviant processing in ASD. It has been observed that children with ASD showed smaller change detection responses relative to typically developing controls, which was further associated with language and sensory symptoms (Ludlow et al., 2014; Roberts et al., 2011). A recent meta-analysis by Schwartz, Shinn-Cunningham and Tager-Flusberg (2018) however, revealed that there was large variability across 22 studies looking at change detection through the classic MMN paradigms, and highlighted small sample sizes and large methodological differences as a potential cause of inconsistencies in the literature. Present findings question whether change detection is a universal characteristic of the early ASD profile and suggest that the response is likely to be dependent on specific stimulus characteristics or individual differences present in the sample.

Results from analysis of auditory habituation responses returned strong effect sizes for effect of Condition (i.e. Standard) when split by Group and Age, ranging .12-.23. Associations between auditory habituation and language development were further supported by confidence intervals that did not cross the zero value. It should be noted, however, that the overall sample size was reduced in these comparisons, as not all infants who had good EEG data had valid behavioural assessments. Relative to studies of similar age populations, present effect and sample sizes suggest that we had enough power to detect a significant difference. However, comparing effect sizes for ERP responses between tasks described in Chapter 4 and 5, the habituation response was not consistent (Figure 5.1 depicts no significant reductions in amplitude between Standard 1,2, or 3). It should be noted that the auditory oddball task was more complex due to unpredictability of the deviant tone (vs. auditory trains where the deviant occurred at the end of the 3-standard tone train), which could explain some differences in the effect sizes reported.

A wholly different response pattern was revealed based in a gamma-driving task in Chapter 6. Contrary to the hypotheses set out for the task, there were no robust ASSR responses detected within the beta or gamma frequency band, nor were there detectable differences in gamma power in infants with elevated ASD/ADHD likelihood or a diagnosis of NF1. The main implications for the wider literature are that (1) frequency-specific responses are difficult to detect in awake infants and (2) there were no group differences in gamma or beta entrainment at 14 months based on familial or monogenic likelihood of neurodevelopmental conditions. In addition, there were no differences in gamma power as reported in Chapter 5. One possible explanation for the inconsistency is the different types of gamma activity that were measured (Rojas & Wilson, 2014). Specifically, the auditory oddball task looked at transient/evoked gamma, while the frequency modulation task examined whether it was possible to drive a sustained auditory response within the gamma frequency range. As the ASSR paradigm was set out as a feasibility study, it is currently difficult to compare the findings to previous literature. Further work is needed to establish the source of these differences as well as possible replication of the study using a wider range of frequency modulation rates and/or outcome data to further understand why it was not possible to detect strong group differences in the task.

7.1.3 Early development in Neurofibromatosis Type 1: identifying common paths to neurodevelopmental conditions.

Data from the first study of infants with NF1 has revealed some important insights into the early development of communication within this population, previously unreported in the literature. NF1 is a monogenic condition (see Chapter 1.6.2.1) with a high prevalence of ASD and ADHD (25% and 50% respectively; Garg et al., 2013; Hirabaru & Matsuo, 2018; Vogel, Gutmann, & Morris, 2017), as well as the reported GABAergic dysfunction in the brain (Costa & Silva, 2002; Violante et al., 2013). Based on the E/I imbalance theory of ASD (Rubenstein & Merzenich, 2003), it was argued that infants with NF1 could provide important insights into

effects of familial or monogenic effects onto development of neurodevelopmental conditions. An initial case series was published on a subset of 10 infants reported a specific developmental profile in NF1 that differed from infants who go on to develop ASD with reduced gross motor and expressive language ability by 10 months of age (Kolesnik et al., 2017). In addition to these preliminary findings, this work used EEG to explore auditory processing differences across individuals with typical development relative to infants with NF1.

An auditory trains task was administered longitudinally, and revealed that 5-month-old infants with NF1 did not show an expected habituation response following repetition of vowels. The finding was consistent with prediction that there were age related changes in speech processing, which fit in to the broader literature on habituation that suggested impairment in a basic learning function may be associated with later impairments in communication and sensory processing abilities (Benasich & Tallal, 1996; Fenckova et al., 2019; Guiraud et al., 2011; McCall & Carriger, 1993). The habituation response, however, was similar between NF1 and typically developing control group at 10 months. This was unexpected based on findings of reduced habituation responses across childhood and adolescence in individuals with rare genetic disorders or later ASD (Ethridge et al., 2016; Fenckova et al., 2019). On the other hand, animal work has suggested that transient alterations within the E/I balance during early stages of mouse brain development have long-term effects on communication and ASD symptomology (Bateup et al., 2013; Lin et al., 2013; Meredith et al., 2012; Selimbeyoglu et al., 2017), which would highlight altered habituation as potential translational mechanism of ASD in NF1. Further work is needed to explore whether initial atypical habituation responses 'recover' between 5 and 10 months of age or whether impaired habituation can prospectively predict developmental outcome in this infant population. As such, larger samples are needed of infants at 5 months of age in order to establish whether reduced/absent auditory habituation is present across all infants with NF1. Findings from the frequency modulation task described

in Chapter 6 did not find gamma or beta ASSR or habituation responses relative to typically developing infants. As highlighted above, the result suggested that the steady-state response may not have matured by 14 months of age. However, this does not negate the finding of atypical habituation in the auditory trains task as fundamentally they were examining different types of gamma activity that may have different developmental trajectories.

Overall, there was reduced habituation in infants with NF1 at 5 months, which may be attributed to an overall dysregulation in functional specialisation in the brain and has implications for research and clinical work. The findings support previous animal work (Bateup et al., 2013; Lovelace et al., 2016; Sinclair, Oranje, et al., 2017) and human studies (Ethridge et al., 2016; Guiraud et al., 2011; Jones et al., 2017), which argued that disrupted habituation was a common pathway over familial/monogenic predictors of neurodevelopmental disorders. This was corroborated by findings from Chapter 5 of this work suggested that children with later ASD showed atypical gamma activation to auditory repetition. The findings further fit it with the growing literature on auditory processing in infants with NF1, including the recently funded project looking at habituation in adolescents with the condition (Lancette et al., 2018). The observation of atypical habituation as early as 5

months in NF1thus has wide implications for the literature beyond current knowledge of early development in this population.

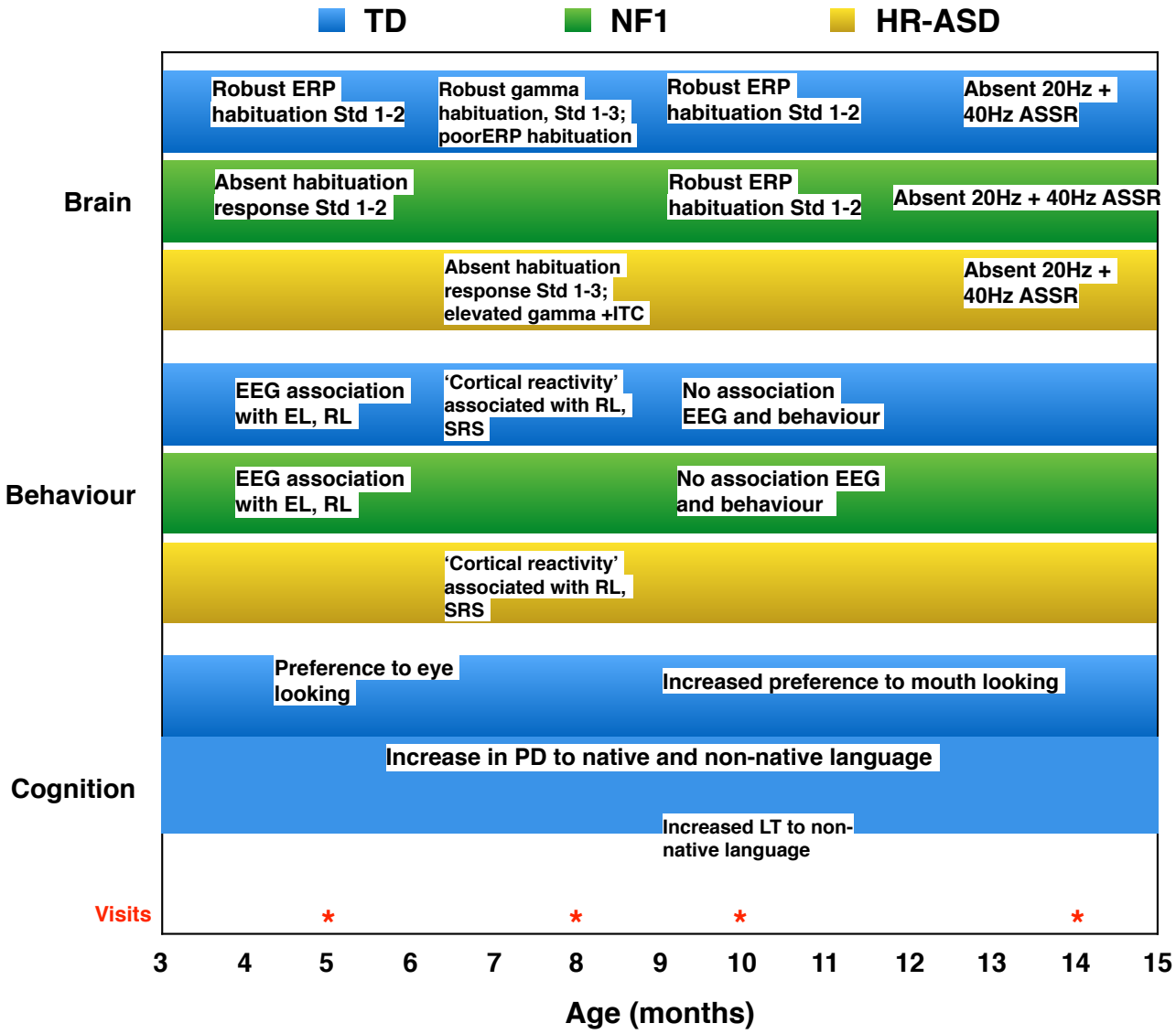


Figure 7.1 Graphical depiction of the findings of auditory and speech perception from this thesis over the first 14 months of life separated by levels of brain, behaviour, and cognition. Notably, there are associations between markers of brain and behaviour. Differences in the nature of the samples studied as well as the range of methodological techniques used means that direct comparisons over time are not possible at this stage. The figure depicts dynamic changes over time across infants with typical development, NF1 and a later diagnosis of ASD, suggesting that the 'static' model of neurodevelopment is not appropriate.

7.2 Implications for Theories of Development

By observing brain and behavioural responses from infants at different age points, as well as employing a longitudinal design, it was possible to explore age-dependent effects on functional brain specialisation. The following section discusses the key findings from the work and highlights how they relate to the three main theories/frameworks of development considered in the General Introduction to this work (see Figure 7.1 for a visual representation of present findings).

Although the series of eye tracking tasks in Chapter 3 showed limited evidence to support effects of experience on perception and preference for native language stimuli, there were strong age effects in pupil dilation and looking time. Findings from both the Active Seeking and Selective Attention tasks may initially support the maturation/experience frameworks, in that infants looking behaviour were largely driven by age. However, the pattern of these effects is not linear (i.e. infants with ALE showed shorter looking time towards the English stimulus while no changes were observed in looking time towards the non-native language). In the selective attention task, looking time to face did not increase until 14 months of age, while peak looks were driven by both age and language experience. It could be argued that complex mechanisms are at play during development of these abilities, such as bidirectional interactions between the infant and the environment. Furthermore, associations between pupil dilation, EEG-based markers of habituation and language outcome supported the assumptions of IS framework, as they highlighted the links between brain and behaviour. Figure 7.1 further depicts emergence of these critical skills in the first 14 months of life. This has implications for research into audiovisual attention, and further replication of these paradigms in necessary to investigate the 'critical periods' in which these skills emerge in both typically and atypically developing infants.

Findings from Chapters 4 and 5 reported marked differences in EEG responses to auditory stimuli in infants with and without elevated familial or monogenic likelihood of developmental conditions. For example, infants with later ASD displayed differences in early auditory processing as early as 8 months of age which were related to behavioural outcome (Chapter 5). By analysing relationships between electrophysiology and behavioural phenotype, it was possible to see that atypical gamma activation was related to ASD-symptomology, which supported previous literature that proposed gamma activity to be an effective therapeutic target (Lee et al., 2016; Port et al., 2017; Rojas & Wilson, 2014; Snijders et al., 2013). On the other hand, the relationship was derived from a correlational analysis, which means that it is difficult to establish causative factors (Bleske-Rechek et al., 2015). Visualising auditory processing and behaviour allows to understand the implications of neural function dimensionally, rather than the dichotomous 'typical' vs. 'atypical' classification, which supports the predictions of the IS and neuroconstructivism frameworks (Johnson, 2000, 2011; Karmiloff-Smith, 2006, 2009).

Based on the preliminary findings from the group of infants with NF1 as well as elevated likelihood of neurodevelopmental conditions ASD and ADHD, it can be argued that there is an emerging pattern of divergent development of auditory processing that has an effect on the speed of emergence of early communication skills (Figure 7.1). Specifically, this can be evaluated based on a review by Johnson and colleagues (2015) discussed above, who proposed that sensory processing is one of the core modules that underlies atypical developmental trajectories. The study has further addressed the researchers' recommendations of considering several different paths to ASD/ADHD development such as single gene disorder NF1 (Garg, Green, et al., 2013; Garg, Lehtonen, et al., 2013). Importantly, we found reduced auditory habituation responses at 5 months in NF1 and in infants with later ASD at 8 months, which suggests that there may be common mechanisms underlying sensory and speech perception difficulties before the age of one, yet the timing of those differences (i.e. earlier in the case of

NF1 than familial ASD) may offer effective treatment targets. One potential issue in the present sample, however, is the disproportionally low numbers of de-novo than familial NF1 mutations, which is an important avenue to consider in future investigations. Further, retrospective analysis of the NF1 sample with additional data for co-occurring ASD/ADHD is necessary to fully assimilate the low-level learning mechanisms to a dysregulation in developmental pathway. The findings further support the concept of 'dynamic' development, as habituation was not consistently found in TD infants across 5-10 months, and further work is needed to establish whether this difference was due to processes beyond task differences.

Notably, there is scope to investigate experiential factors further, including parent SES, amount of language exposure (including variability and quality), which may provide greater information about the direct effects of the environment on early communicative abilities. Outcome data, including diagnosis and language level at age 3 will be a particularly important avenue for future investigation. We will be able to retrospectively observe (as was done in Chapter 5). Future studies should focus on examining the trajectories of development on an individual level, which would require larger sample sizes in order to better understand likelihood and protective factors between genetic conditions and elevated incidence of neurodevelopmental conditions.

There was some evidence for localisation of responses, which is one of the core assumptions of the IS framework, although the expected hemispheric asymmetry was not observed in several of the studies. There were also no significant differences between the region/hemisphere of the habituation response in Chapter 4, which suggested that there was limited evidence for an increase in localisation of response in the sample tested. However, due to somewhat poor spatial resolution of EEG, MEG or fMRI techniques with analogous auditory paradigms may help to address the localisation predictions within the IS, and should be considered in future studies.

7.3 Limitations and Practical Considerations

Next, I consider the overall limitations of the present work, in addition to the specific limitations that were discussed in chapters above. Firstly, it can be argued that the sample sizes used for several tasks were underpowered to show significant group effects (see ALE group in Chapter 3, EL-ASD in Chapter 4 or NF1 group in Chapters 4 and 6). Infants with additional language experience (ALE) were not the primary objective of the investigation, and were used only to supplement results from the total sample of typically developing infants to show variation and possible effects of early language experience on looking behaviour. Nonetheless, presence of group effects was further supported by dynamic behavioural analysis, where EEG and eye tracking indices were dynamically related to examiner/parent-rated levels of language ability irrespective of group status.

There are some considerable limitations to using infant populations. These included practical considerations such as high attrition rates for different tasks due to (1) tiredness or (2) intolerance of testing equipment such as the EEG net, as well as increased noise in data due to movement relative to studies of children and adults. Additionally, the use of longitudinal design in studies described throughout the thesis may be limited by practice or cohort effects. Due to only slight changes in testing protocols between visits and the young age of participants, practice effects during task performance are less likely. By looking at sensory brain function, was also possible to minimise cohort effects (i.e. effects that may influence findings based on the particular point in time at which the infants are recruited and tested, in 2019 or 1990), although they may still affect the way parents report on their child's behaviour.

One pertinent issue to samples recruited for both GABBLES and BASIS studies, however, is participant self-selection. In developmental studies, families and parents of children from more educated, financially stable backgrounds are more likely to volunteer. This is particularly detrimental for studies of familial ASD, as families of children with more severe

symptoms are less likely to take part and therefore only reflect a small subsection of the ASD phenotype (French & Kennedy, 2018; Russell et al., 2019). Self-selection bias makes determination of causation more difficult, and further work is required to assess individuals from a wider range of socio-economic backgrounds. This is less likely to apply to the sample of infants with NF1, which have been recruited from all over the UK following referral from the National Health Service (NHS). However, families with children or caregivers with less severe neurological or physical impairments are more likely to be able to attend laboratory visits. Participant self-selection bias is particularly important to developmental research and calls for generation of protocols that would be easily integrated in the community or the home environment (for methodological examples of infant testing see Goodwin et al. (2016) for eye tracking and Lau-Zhu, Lau, & McLoughlin (2019) and Sahi et al. (2014) for discussion of wearable EEG in the home).

7.3.1 Recommendations for future infant research.

Present work further revealed important avenues for future infant research as well as specific considerations for interpretation of existent literature on brain development. Irrespective of the wealth of evidence on infant specialisation towards the native language, looking at gaze data alone did not reveal significant group or language experience effects. Pupil dilation data added some important information about processing of visual stimuli, and should therefore be examined in eye tracking studies (rather than using basic gaze metrics such as looking or reaction time). Moreover, adding behavioural and ERP measures may improve the predictive value of eye tracking measures. Further work should look at the joint correlates between gaze/pupil activity and ongoing EEG activity in order to better understand the neural generators of this response in both typical and atypical neural systems.

In addition to using the traditional ERP technique to measure infant cognitive processing, different approaches to time-frequency analyses described in Chapters 5 and 6

allowed a more complete view of the brain response by decomposing the overall signal into different frequency bands. Studies described in this work have shown stable activity in the gamma band in awake infants. Robust group effects of gamma atypicalities and their relation to sensory and communication domains further support the use of gamma as an EEG-based index of neurodevelopmental conditions, which is widely supported in the literature (Jeste, Frohlich, & Loo, 2015; Rojas & Wilson, 2014; Varcin & Nelson, 2016). However, the frequency modulation task described in Chapter 6, specifically designed to 'drive' the gamma band response did not yield robust frequency band or group effects. Inconsistencies across findings presented in this work, concur with the overall debate as to the utility of EEG-based markers in predicting developmental outcome (Dickinson et al., 2016). Nonetheless, ADHD training trials have shown associations between degree of change in EEG and self-reported improvements in pain, mood and sleep (Gevensleben et al., 2009; Mueller, Donaldson, Nelson, & Layman, 2001; for review see Jeste, Frohlich, & Loo, 2015), which highlights the clinical utility of further study of auditory processing indices.

7.3.2 Practical implications and recommendations for clinicians and researchers working with infants with NF1.

In addition to looking at infants with familial likelihood of ASD, this thesis presented results from the first electrophysiological studies of development in NF1. Findings from Chapter 4 suggest that there may be differences in auditory processing from as early as 5 months of age, therefore detection and diagnosis of the condition is important for potential interventions to be delivered. Late identification and diagnosis of sporadic NF1 are prevalent in the UK, and links between NF1 and ASD have been debated since the 1980s (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators & Centers for Disease Control and Prevention, 2007; Bilder et al., 2016; McKeever et al., 2008). Therefore, characterising ASD in NF1 is an important next step in our

work. Researchers and clinicians should also note the overall lower developmental ability across all major behavioural domain in this population and focus on identifying particular abilities or behaviours that may have additive or protective effects on later cognitive outcome.

There are considerable limitations of looking at NF1 in developmental research as well as using a rare genetic disorder to identify paths to ASD. One of the main difficulties in working with the population is the delay in diagnosis that occurs in many cases of spontaneous NF1. Difficulty in obtaining participants was alleviated by collaboration with University of Manchester, where there is access to newly diagnosed NF1 patients through NHS referral to the NF1 clinic (coordinated by Professor Jonathan Green and Dr Shruti Garg). As the study is ongoing, it will be important to consider differences in severity of the behavioural phenotype and sensory electrophysiological responses in infants with or without previous family history of NF1. Further, the NF1 cohort was used to identify common pathways in familial versus monogenic likelihood of neurodevelopmental conditions, which is a somewhat novel approach in the field. It has been suggested that using this methodology may help understand the complex heterogeneity of neurodevelopmental conditions such as ASD, which have previously been overlooked in adult or animal work (Ruggeri et al., 2014; Varcin & Jeste, 2017). In addition, prospective studies allow to study infants before any behavioural symptoms of neurodevelopmental conditions emerge, thereby providing more information about potential critical periods in which interventions can be delivered (French & Kennedy, 2018; Goodwin et al., 2016; Green et al., 2010).

Nonetheless, the gamma-driving task described in Chapter 6 did not reveal differences between infants with NF1 and typically developing controls, although neighter group showed effects of entrainment. In order to better understand the influence of genetic and familial factors on frequency modulation or habituation would be to collect much larger sample sizes for each group or identifying a ‘typical’ response in a sample of infants/children without history of

neurodevelopmental or genetic conditions. Nonetheless, present work features relatively large samples of infant sibling groups as well as a large group of infants with NF1 relative to previous studies of rare genetic disorders.

Another prevalent issue, is the use of NF1 as a genetic model of atypical neurodevelopment. Findings from mouse and infant studies of Tuberous Sclerosis Complex (TSC) have shown that there are specific targets in the brain or biomarkers including overconnectivity and organisation of white matter tracts that predicted severity of symptoms of ASD in TSC (Jeste & Geschwind, 2014; Jeste et al., 2014; Peng, Lee, Wang, & Huang, 2004; Widjaja et al., 2010). Further, researchers were able to put forward therapeutic targets for reduction of communication and learning difficulties in mice (Ehninger et al., 2008). These results provided rationale to study NF1, where there is increased incidence of ASD without additional complications of seizures (Kandt, 2003). Yet, although it is known that up to 50% of children and adults with NF1 experience cognitive and behavioural difficulties (Millichap, 2002; North et al., 2002; Vogel et al., 2017), the incidence rates of developmental disorders such as ASD and ADHD in NF1 have large variations across different studies. For example, different studies reported incidence rate of ASD in NF1 to vary between 2 and 25% (Bilder et al., 2016; Eijk et al., 2018; Garg et al., 2013), which may be explained by differences in assessment and recruitment methods. Due to the current lack of outcome data for the NF1 or STAARS cohorts, it is not possible to estimated prevalence rates of ASD and/or ADHD, although this will be addressed once the outcome data is collected during the 3-year visit.

7.4 Conclusion

From the studies that were conducted as part of this thesis, I concluded that functional specialisation of the brain and atypicalities within this process could be detected from auditory habituation responses as well as age-dependent changes in pupil dilation to natural speech. EEG offers an opportunity to measure different aspects of brain activity non-invasively in

infant populations as well as different ways in which the signal can be interpreted. Sensory markers of auditory processing may be used as predictors of later cognition and developmental outcome, with longitudinal and prospective studies to be at the forefront of future research. These conclusions are particularly valuable to the literature on neurodevelopmental conditions, as I argue that early markers of brain development should be used to identify potential atypicalities in later communication ability, rather than observing differences in overt behaviours i.e. face looking or gaze following, which may appear typical in infants with later ASD. However, not all auditory markers were sensitive to familial and monogenic likelihood of neurodevelopmental conditions, and there is need for future work in design of robust EEG paradigms to be utilised in prospective study designs. Further work is needed to evaluate test-retest reliability as well as age-related changes in these putative EEG-based markers. Lastly, I reported first evidence of atypical repetition and change processing in infants with NF1, which may provide a useful avenue for treatment targets that affect GABAergic signalling pathways in both research and clinical settings.

Appendix A.*Threshold Artefact Detection Tool settings.*

(Netstation 4.5.6 tool specification)

Operation – Bad Channels;

Max-Min > 200uV, Moving average of 80ms on entire segment

Operation – Eye Blink;

Max-Min > 140uV, Moving average of 80ms

Operation – Eye Movement;

Max-Min > 55uV, Window size 640ms, Moving average of 80ms.

Appendix B. *Language Experience interview.*

Timepoint: ID_____ Date___/___/___ Interviewer_____ Respondent A B C Other

Languages (to be completed at every Time Point)

Of all the languages your participating infant hears, what proportion is in each language?

Languages (please list)	**Proportion heard by child at home (from 0% to 100%)**	**Proportion heard by child elsewhere (e.g. at nursery)**
English		

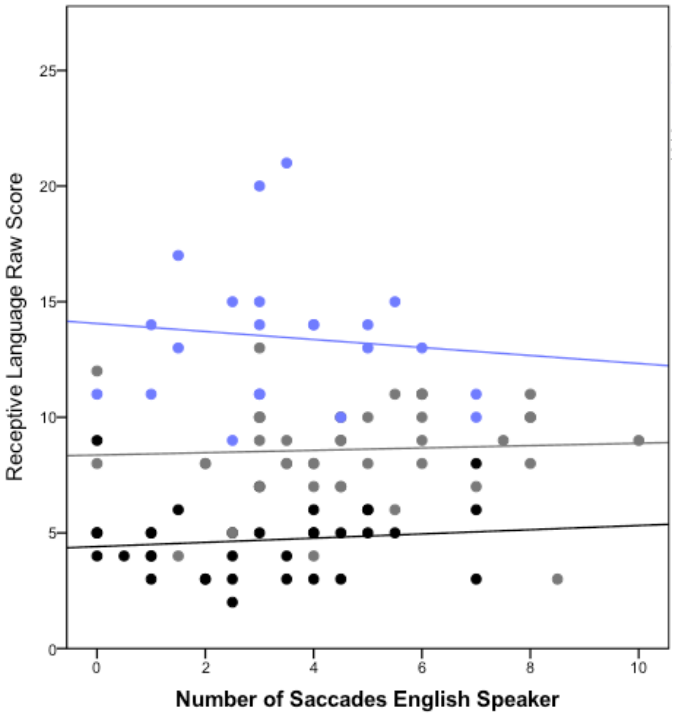
Have these proportions changed over time since the child was born? ***(if so, please note ages and exposures).***

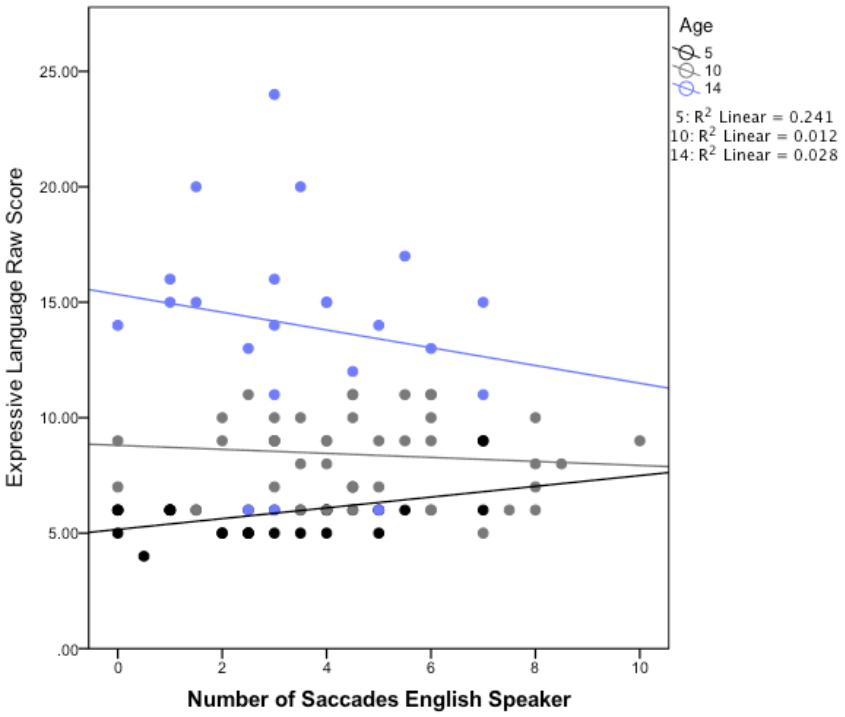
If your participating infant speaks, what proportion of speech is in each language?

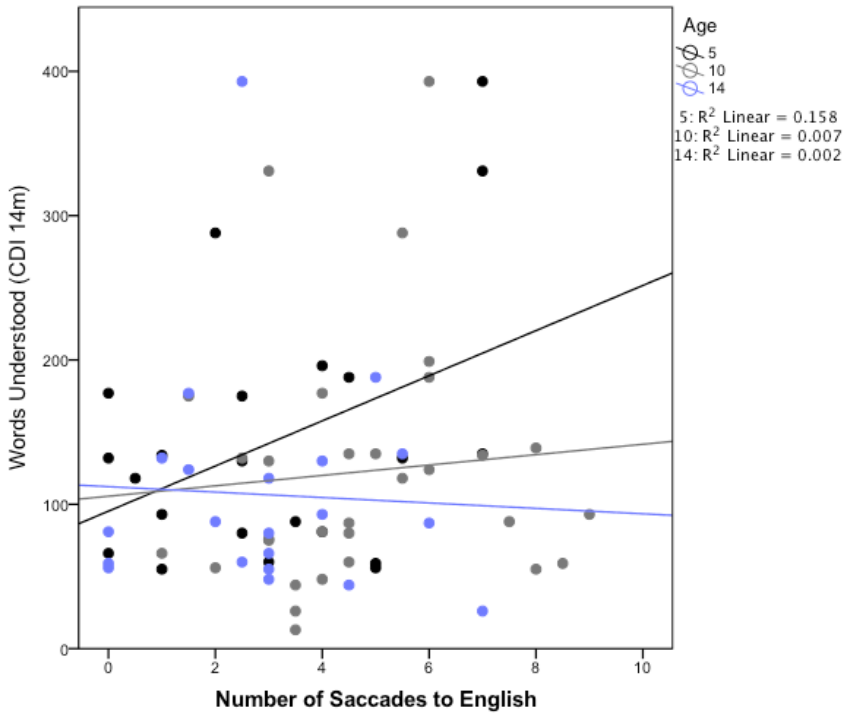
Language (please list)	**Proportion of Speech by Child (from 0% to 100%)**
English	

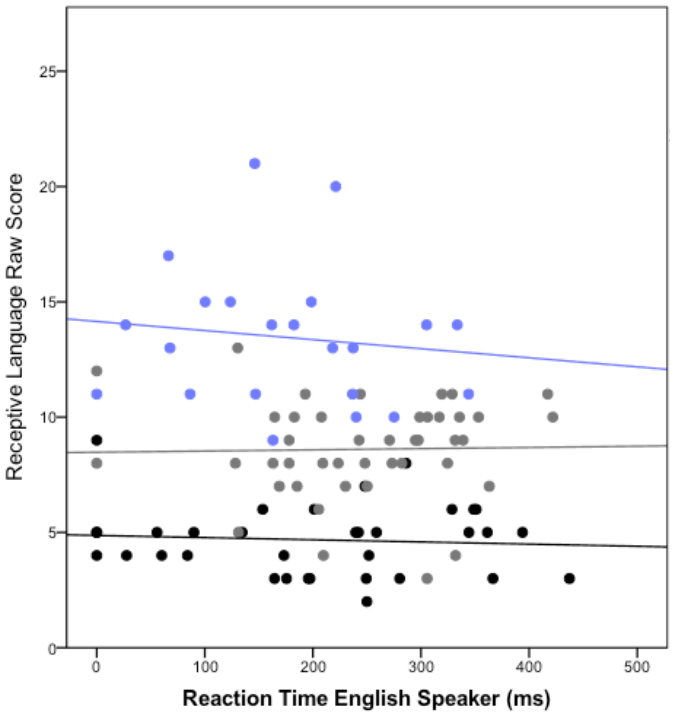
Has this changed over time since the child first started speaking? ***(if so, please note ages and pattern).***

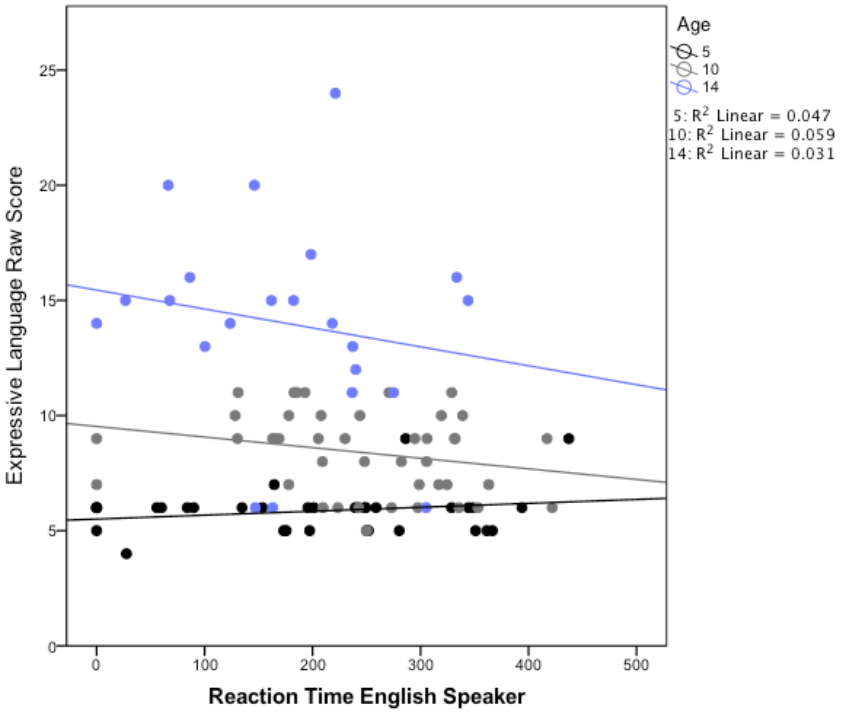
Appendix C. *Individual scatterplots: active seeking and standardised measures of language ability.*

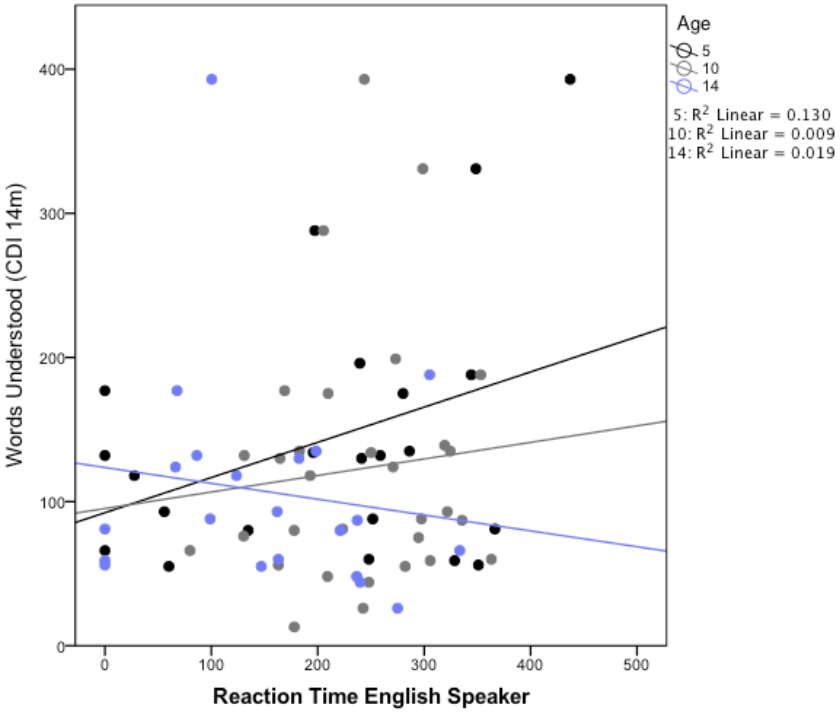


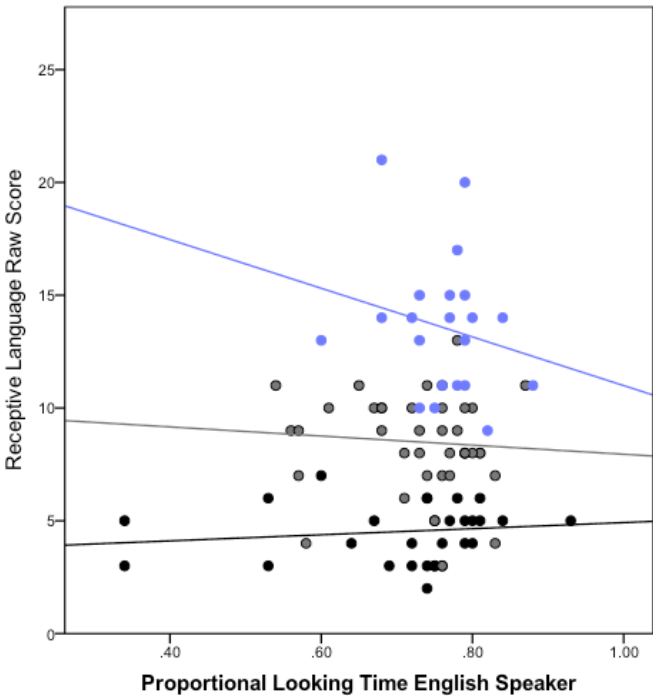


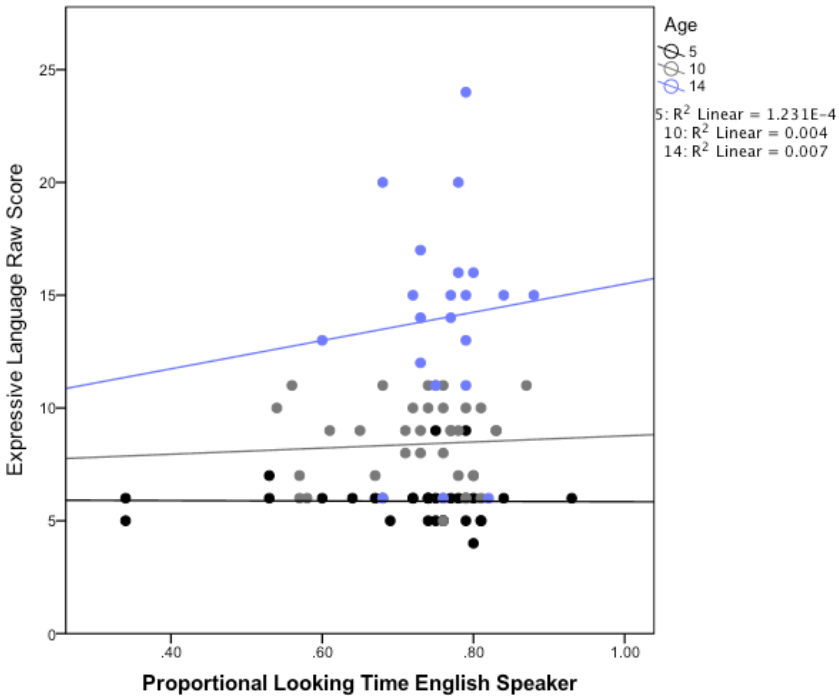


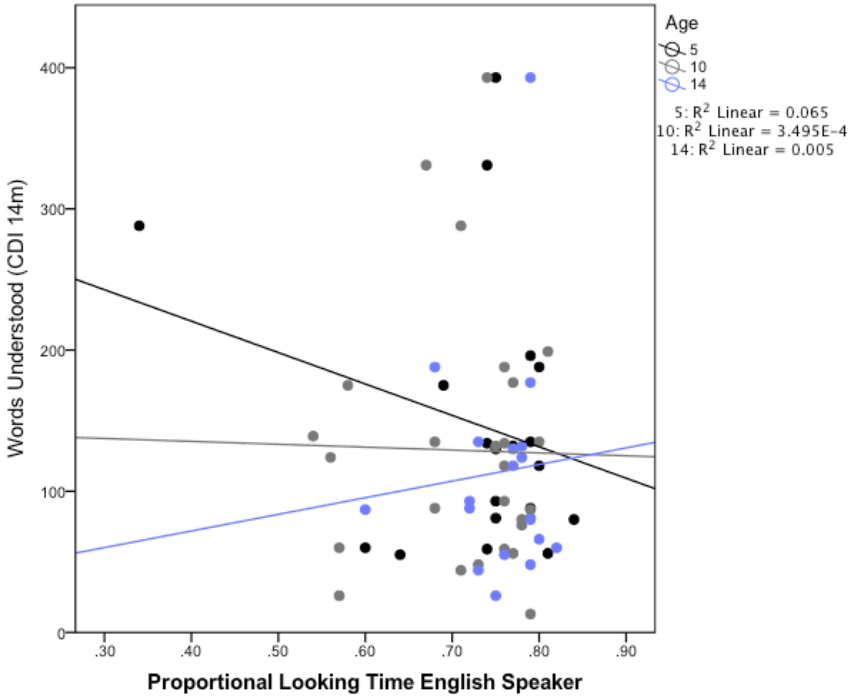

Receptive Language Raw Score
Reaction Time English Speaker (ms)
0
5
10
15
20
25
0
100
200
300
400
500


Expressive Language Raw Score
Reaction Time English Speaker
Age
5
10
14
5: R² Linear = 0.047
10: R² Linear = 0.059
14: R² Linear = 0.031
0
5
10
15
20
25
0
100
200
300
400
500

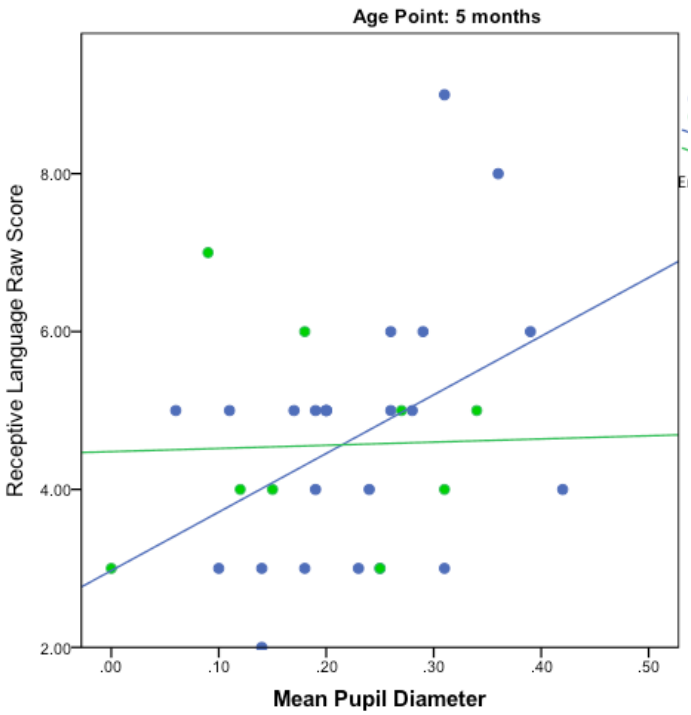

Words Understood (CDI 14m)
Reaction Time English Speaker
Age
5
10
14
5: R² Linear = 0.130
10: R² Linear = 0.009
14: R² Linear = 0.019
0
100
200
300
400
0
100
200
300
400
500

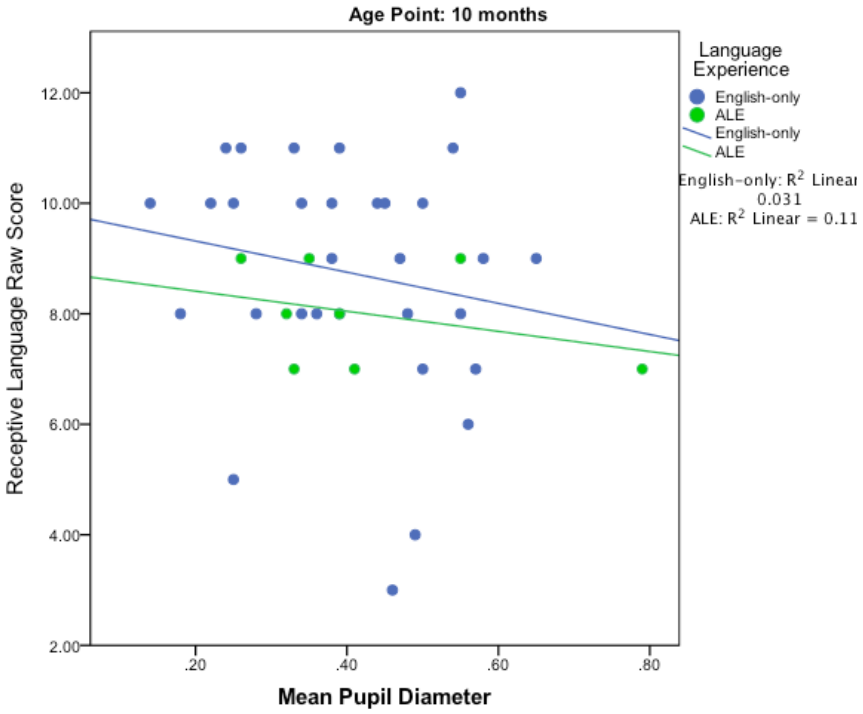

Receptive Language Raw Score
25
20
15
10
5
0
.40
.60
.80
1.00
Proportional Looking Time English Speaker

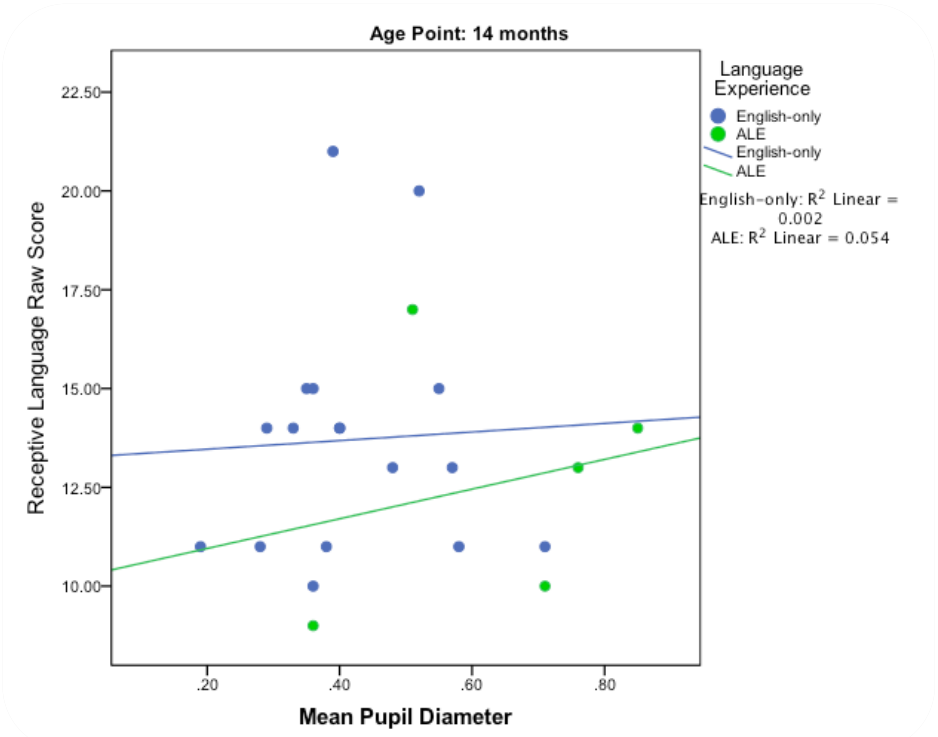

Expressive Language Raw Score
25
20
15
10
5
0
.40
.60
.80
1.00
Proportional Looking Time English Speaker
Age
5
10
14
5: R² Linear = 1.231E-4
10: R² Linear = 0.004
14: R² Linear = 0.007

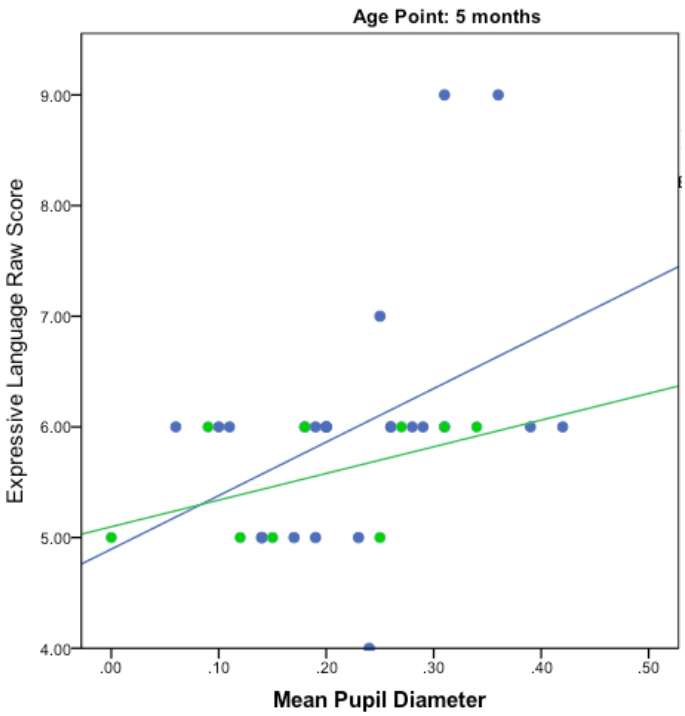

Words Understood (CDI 14m)
400
300
200
100
0
.30
.40
.50
.60
.70
.80
.90
Proportional Looking Time English Speaker
Age
5
10
14
5: R² Linear = 0.065
10: R² Linear = 3.495E-4
14: R² Linear = 0.005

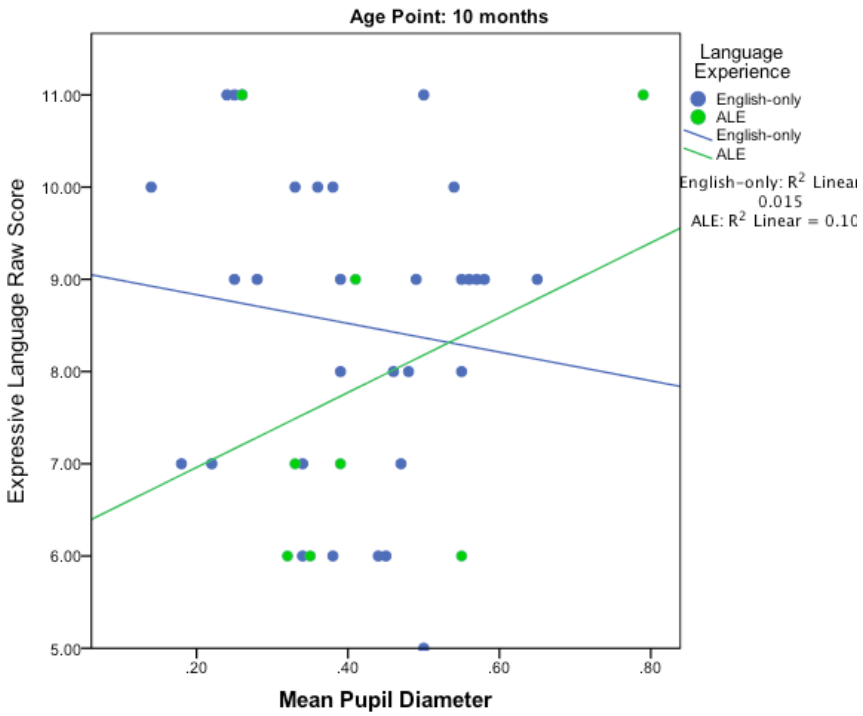
Pupil dilation scatter plots were further split into language experience (English-only vs. ALE) and age.

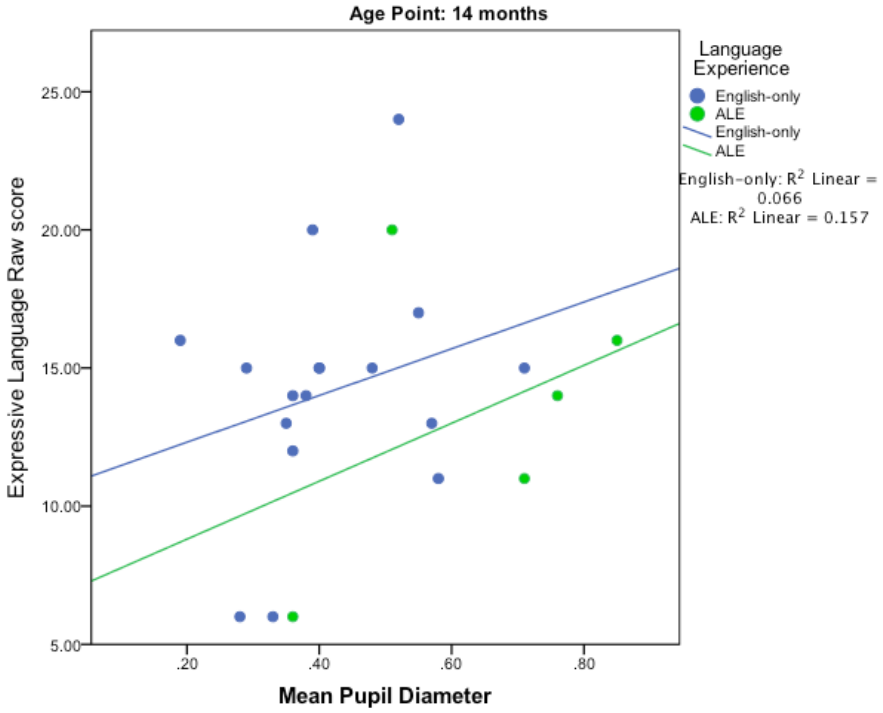


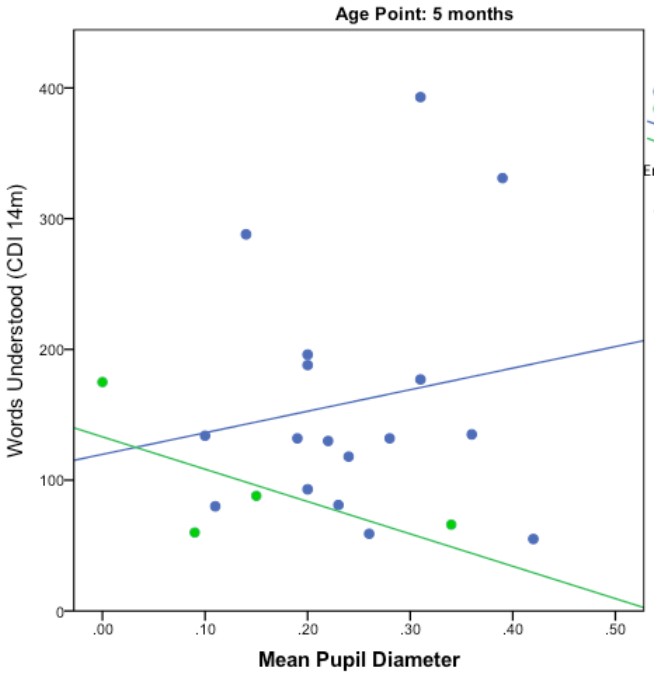


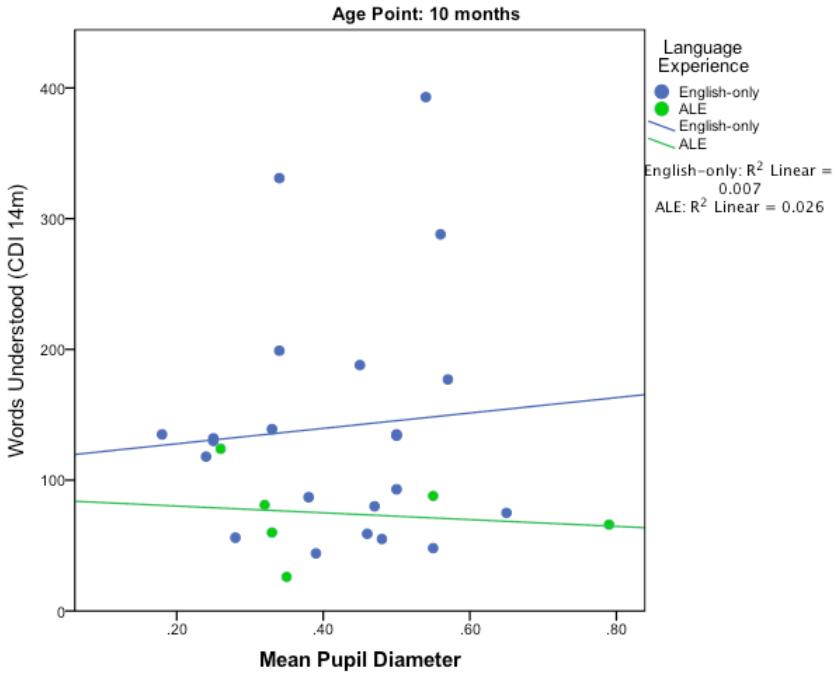


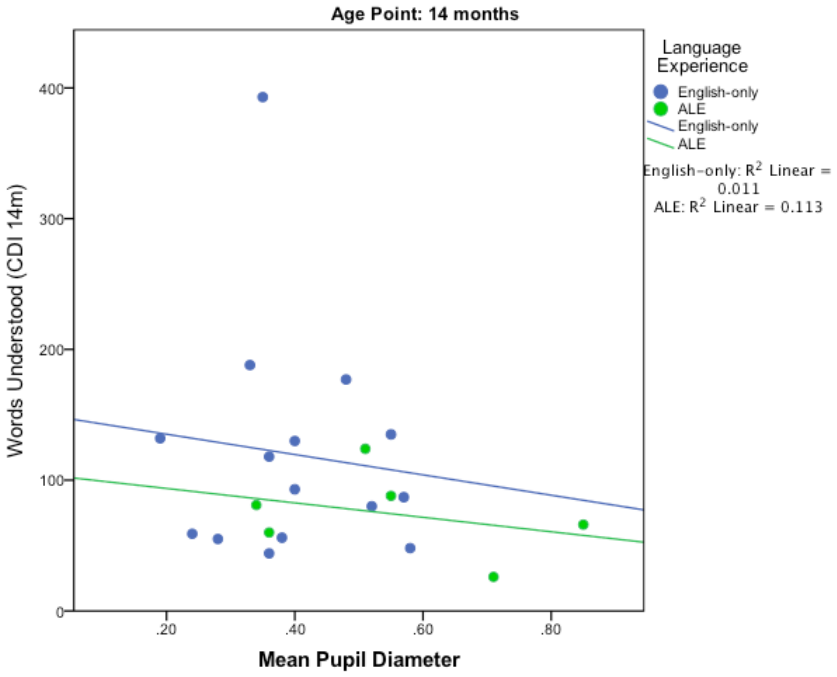

Age Point: 5 months
Expressive Language Raw Score
9.00
8.00
7.00
6.00
5.00
4.00
.00
.10
.20
.30
.40
.50
Mean Pupil Diameter


Age Point: 10 months
Expressive Language Raw Score
11.00
10.00
9.00
8.00
7.00
6.00
5.00
.20
.40
.60
.80
Mean Pupil Diameter
Language Experience
English-only
ALE
English-only
ALE
English-only: R2 Linear 0.015
ALE: R2 Linear = 0.10


Age Point: 14 months
Expressive Language Raw score
25.00
20.00
15.00
10.00
5.00
.20
.40
.60
.80
Mean Pupil Diameter
Language Experience
English-only
ALE
English-only
ALE
English-only: R2 Linear = 0.066
ALE: R2 Linear = 0.157


Age Point: 5 months
Words Understood (CDI 14m)
Mean Pupil Diameter
0
100
200
300
400
.00
.10
.20
.30
.40
.50


Age Point: 10 months
Words Understood (CDI 14m)
Mean Pupil Diameter
0
100
200
300
400
.20
.40
.60
.80
Language Experience
English-only
ALE
English-only
ALE
English-only: R2 Linear = 0.007
ALE: R2 Linear = 0.026


Age Point: 14 months
Words Understood (CDI 14m)
Mean Pupil Diameter
0
100
200
300
400
.20
.40
.60
.80
Language Experience
English-only
ALE
English-only
ALE
English-only: R2 Linear = 0.011
ALE: R2 Linear = 0.113

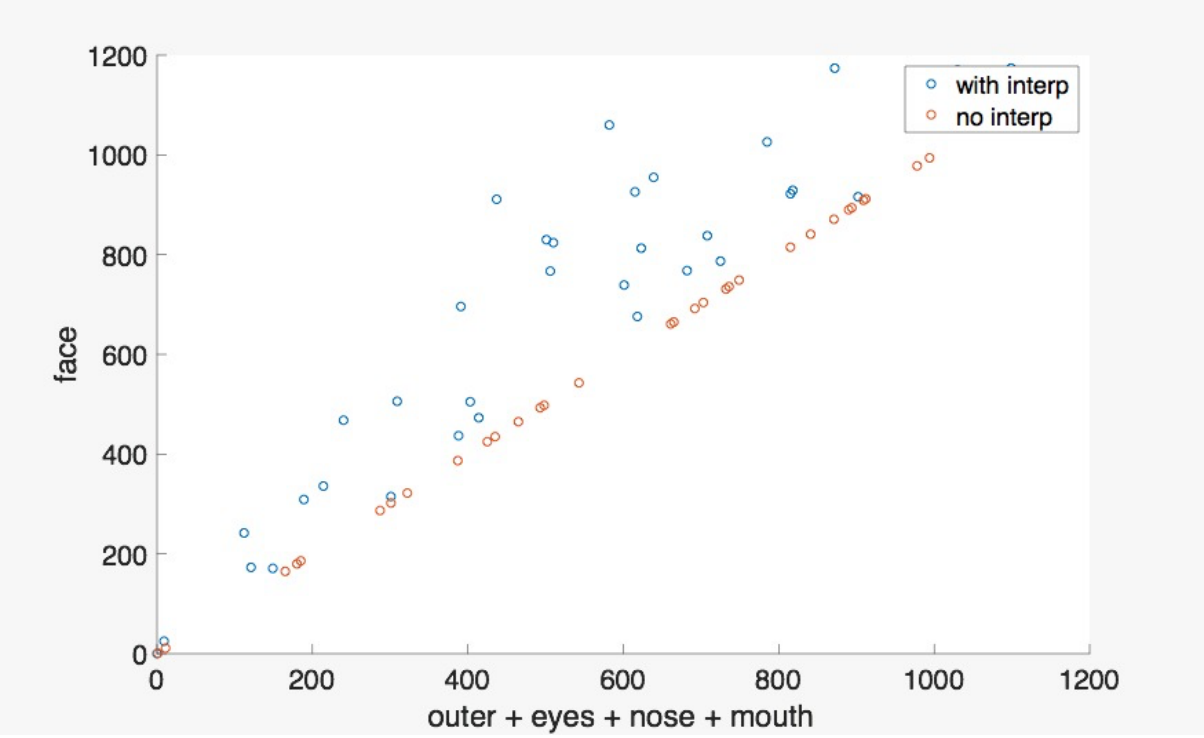
Appendix D.*Data quality Audiovisual Matching task.*

Table B. *Descriptive data for number of trials retained with conservative criterion of less than 30% data loss. Note that the biggest change is reduction in sample size at 5 and 10-month Age Points rather than average trials remaining.*

Age Point (N visits)	*30% Prop Data Lost*			*Data Retention %*
	n	*Match*	*Predict*	
5m (45)	18	14.11 [1.96]	15.05 [1.54]	40%
10m (48)	25	14.04 [2.24]	15.17 [2.27]	52%
14m (31)	24	14 [2.35]	14.73 [2.58]	77%

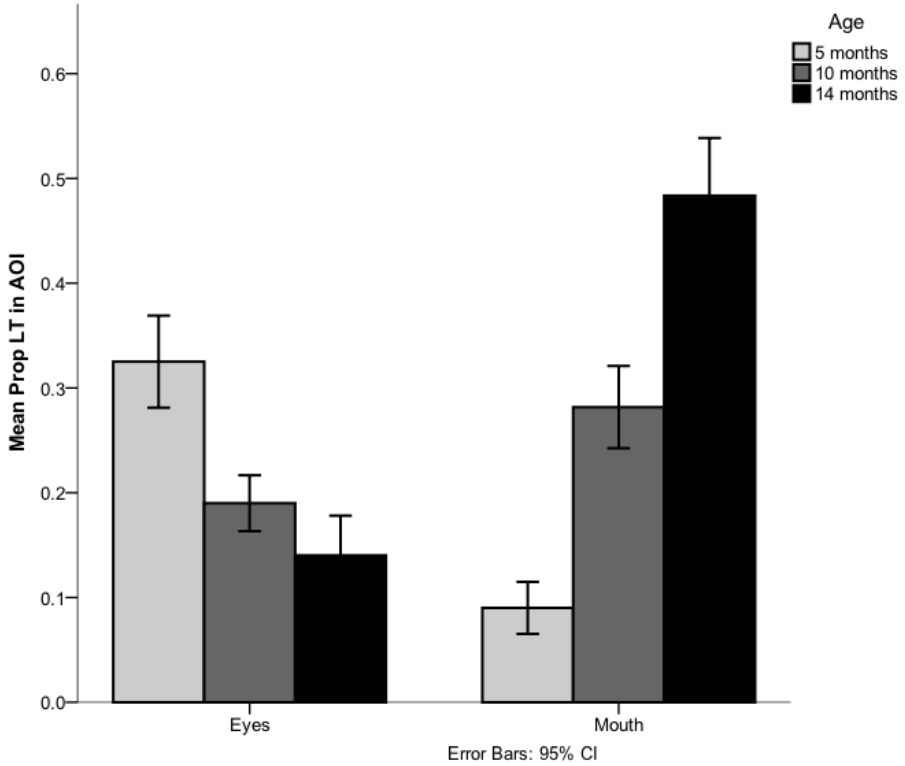
Table B shows the retention rate per group based on the inclusion criterion of 30% proportional data loss for the average prediction paradigm (Task 2). The more lenient criterion of 50% was used in the final analysis in order to maximise retention rates for these relatively small groups. As the same infants were tested across Task 1-3, it could be suggested that this task was particularly cognitively demanding/not as engaging as the others, which resulted in higher rate of data loss. High attrition was particularly apparent in the 5-month group and increasing the inclusion rate resulted in 44% of the sample being conserved after the cleaning steps. This was likely due to the small age of the infants and difficulty in getting sufficient calibration. Note that 50% data retention rate has been found adequate for the age-range and study type (Francois et al., 2018; Gredebäck et al., 2009; Oates, 1998).

Appendix E.*Overestimation in PropLT between Face AOI and the interpolated sum of its parts.*



Scatterplot visualising the difference in output of the interpolation between Prop LT to the Face AOI versus the sum of face components, including Eyes, Nose, Mouth and Outerface AOI. As can be seen from the plot, sum of face components without interpolation is directly proportional to LT to the face. However, when feature data is interpolated, the sum of its parts is lower than the total LT to the face. This is because the face AOI is larger than the component parts and therefore has more opportunities to interpolate gaps of missing data.

Appendix F. *Age-dependent changes in looking towards the eyes and mouth.*



Bar plot showing age-related changes in looking towards the Eye and Mouth AOI in the Nursery Rhymes task. The data suggests an inverse relationship, as looking moves away from the eyes and to the mouth. This is important to visualise alongside the ETM ratio described in the Chapter 3, as it shows that looking to the Mouth at 14 months is much stronger than looking to the Eyes at 5 months, which is in contrast to previous reports who suggest high levels of looking to the Eyes in both younger and older infants.

Appendix G. *Pre-registration Auditory Trains Task.*

Study information
Title
Auditory processing and language development in infants with Neurofibromatosis Type 1

Authors
Anna Kolesnik*
Jannath Begum Ali*
Isabel Quiroz
Luke Mason
Shruti Garg
Jonathan Green
Mark Johnson
Emily Jones
& BASIS and EDEN teams
*Joint first authors

1. Research Questions
How do infants with Neurofibromatosis Type 1 [1] differ from the typical population on the common metrics of auditory processing (i.e. habituation, change detection)?, [2] can we detect age-related changes in oscillatory activity in these populations , and [3] are these changes related to individual variability in early language development?

2. Hypotheses
Neurofibromatosis Type 1 (NF1) is the most common monogenic disorder, with notable cognitive and behavioural difficulties. NF1 has been reported to have up to 25% prevalence of Autism Spectrum Disorders (ASDs) and 45% broader autism symptomatology (1–4). This is accompanied by GABAergic imbalances in brain circuitry (5,6), as well as delays in language acquisition (7,8). This study represents the first investigation of neural function in infants with NF1, and will supplement existent literature on atypical development in this population. Overall, it is expected that infants with NF1 will show patterns of auditory processing similar to infants with a later diagnosis of ASD (9,10) relative to the neurotypical controls. Note that the current lack of research in infants with this condition means that very little is known about their early developmental profile or neurophysiological function.

Age differences and individual trajectories will be measured at two levels:

2.1. Neural
Expected age and group effects are outlined below and the predictions are outlined initially for the typically developing infants, followed by those with an NF1 diagnosis. All infants were presented with an auditory trains task, comprised of three repetitions of one vowel, followed by either a pitch or a vowel deviant. For task details and identification of temporal and spatial regions of interest see Appendix 1.

2.1.1. *ERP analysis*:

2.1.1.1. *Habituation.* We expect a clear reduction in first positive peak response (50-200ms) from ERP data between across the three Standard tones in infants with typical development. Infants with

NF1 are expected to show reduced average ERP response based on findings of reduced or absent habituation responses in individuals with elevated risk of ASD and genetic conditions (9,17–19).

2.1.1.2. *Vowel/pitch change.* We further expect that there will be an increase in the later negativity response (250-400ms) between the vowel/pitch deviants and the third repetition of the standard as has been shown previously in typical development (20,21). We predict that this response will show age-related changes (22), and that it will be reduced in amplitude in infants with NF1 (18).

2.1.2. *Power analysis:*

2.1.2.1. *Habituation.* Following three repetitions of the 'standard' vowel in infants with typical development, we expect to observe habituation, i.e. a dampening of response, through evoked and induced gamma and theta band power. This response is expected to show sensitivity with age (i.e. the difference within the gamma and theta evoked power between Standards and Deviant tones at 10 rather than 5 months). ERP responses have been found to be reduced in amplitude and have clearer peaks with age (see 2.1.2.1.), gamma responses have been found to decrease in amplitude between childhood and adulthood (11), which is what we expect to see between 5 and 10 months of age in the typically developing group. We expect this habituation response to be weaker in infants with NF1 at both age groups, which has been reported in Fragile X (12), with no clear age differences.

2.1.2.2. *Vowel/pitch change.* We expect elevated power responses to Deviant stimuli than Standard in infants with typical development (13). At 10 months, we further expect larger differences in responses between the Vowel and the Standard rather than Pitch change and the Standard, which has been associated with acquisition of language (14,15). Infants with NF1 are expected to show an attenuated or absent change in response towards vowel and pitch deviants relative to the Standard tones(12,16).

Note the similarities between predictions for the two EEG processing techniques. We expect stronger responses in the same direction from time/frequency(power) decomposition due to higher sensitivity to detect differences in neural responses vs. the grand average of the signal denoted by the classic ERP analysis (23).

2.2. Behavioural

The task and hypotheses described above are assumed to reflect acquisition of auditory expertise (i.e. ability to ignore repeated stimuli, increased attention to global rather than local differences in vowel sounds). Observer and parent report measures of early language will be used to look at associations with identified markers on the auditory trains task. It is expected that EEG-indices

will be sensitive to individual differences in language skill and group (NF1 vs. TD controls).

3. Sampling Plan

3.1. Existing data

Registration prior to analysis of data. As of date of submission, the data exists partly and has been accessed from pilot subjects to ensure data quality. However, no analysis has been conducted related to the research plan.

3.2. Explanation of the data

3.2.1. Brain responses (EEG) to auditory paradigm in infants at 5 and 10 months of age. Data collection is complete for the TD group and is nearing completion for the NF1 group. An analysis pipeline is being developed. Some preliminary cleaning has been done on a small portion of the data (<5%) to validate the paradigms. Data has not yet been analysed or summarised.

3.2.2. Observer ratings of Expressive and Receptive Language (Mullen, 1995) at 5 and 10 months. Data collection and entry is nearing completion. Data has not been analysed or summarised in reference to the EEG data.

3.2.3. Parent report of infant temperament at 5 and 10 months (24) as well as language comprehension and production at 14 months to be used as an outcome measure of language comprehension and proficiency (through the MacArthur-Bates Communicative Development Inventory, CDI; (25)). Data collection is underway. Responses have not been coded, analysed, or summarised.

3.3. Data collection procedure

Thirty infants with NF1 were recruited through local and genetic centres as part of the Early DEvelopment in NF1 (EDEN) study. All participants had their diagnosis confirmed via molecular testing of cord blood samples or clinical diagnosis based on NIH consensus criteria and had no other developmental concerns at the time of the visits. All of these infants were from English speaking households. At 5 months 15 infants attended the visit and 11 EEG datasets were required, while 23 attended the 10-months visit and 19 of those infants completed the EEG protocol. Note that 4 infants recruited for each time point took part in the pilot version of the protocol, where no EEG was administered.

Additionally, 52 control participants (23 male) were recruited for a separate longitudinal study running from November 2016 to March 2018, from a volunteer database at the Centre for Brain and Cognitive Development in Birkbeck University. All children recruited for the study were full term (gestational age >36 weeks) and with no developmental or genetic disorders reported in siblings or first degree relatives. Fourteen infants were recruited from multilingual households, however infants had to hear at least 30% English in the home to be recruited for the study. Infants who had more than 30% of a non-English language experience in the home environment were further classified as having additional language experience (ALE; see *6.5 Exploratory Analyses*). At 5 months of age, 49 infants completed the visit, with

45 taking part in the EEG protocol. At the 10-month visit, 46 infants attended and 46 EEG recordings were made.

The difference in numbers between total visits and EEG recordings can also be justified by non-compliance with the EEG net or tiredness of the infants. At present time, the data is being analysed so the final numbers of 'good' datasets are not available at this stage.
All participant families were reimbursed expenses for travel and subsistence if required. Infants were given a certificate and a T-shirt after each visit to the centre.

3.4. Sample size
The projected sample size is 82 infants (30 NF1; 52 controls).

3.5. Sample size rationale
The chosen sample size is based on recruitment and resource constraints, as well as previous studies. The projected sample will give 0.9% power to detect an estimated global effect of 0.8 at alpha equal .05, in a General Linear Model with 3 response variables. For data exclusion criteria see Section 6.3.

3.6. Stopping rule
For this analysis, data collected from NF1 infants as part of the EDEN study (Early DEvelopment in NF1; http://research.bmh.manchester.ac.uk/socialdevelopment/eden/) will be used for analysis, including all infants with usable data collected until April 2019. Data collection for the typically developing control group has been completed as part of the GABBLES (GAmma and Brain-Based LanguagE Specialization) study between November 2016 and March 2018 (AK, IQ).

4. Variables
4.1. Manipulated variables
N/A
4.2. Measured Variables
4.2.1. Neural (EEG measures)
Raw EEG signal will be processed based on criteria outlined in Appendix 1. All data will be pre-processed in NetStation (EGI, Version 4.5.6). The final averaged data sets will be exported into Excel to produce ERP waveforms. Bad channel replaced data will be exported to Matlab® for time-frequency analysis using wavelet transformation and inter-trial coherence (ITC) calculations using functions from EEGLAB (https://sccn.ucsd.edu/eeglab/), Fieldtrip (26), and in-house scripts.

4.2.1.1. ERP analysis
4.2.1.1.1. *Habituation.* This response will be measured through changes in mean amplitude of first positive peak (50-200ms; associated with fundamental mechanisms of human attention) in the grand average waveform as a

subtraction between Standard 1, 2 and 3. Due to large individual variations in latency and peaks, this analysis will use the average voltage values on selected ROIs (Figure 2).

4.2.1.1.2. *Change detection.* For measures of auditory change responses, both the first positive peak as well as a later ERP component (associated with increased attention following change) which will be obtained by subtracting ERP of the third Standard in the auditory train from ERP to deviants, averaged over 50-200ms and 250-400ms time windows. Note that the present task differs from classic MMN/oddball paradigms used in infants studies of auditory processing (27) This was done to maximise number of trials from Deviant tones and in order to assess the low-level mechanisms of phonological change detection, based on original work from Dehaene-Lamberts and Baillet (28).

4.2.1.2. Power analysis (Habituation and Vowel/pitch change)

4.2.1.2.1. *Evoked power* differences will be extracted using wavelet transformation. The analysis will focus on responses in frontal and tempo-parietal regions in both hemispheres, based on previous work with preverbal infants. Evoked power will be extracted between 50 and 300ms post-stimulus onset. Differences will be examined between Standard 1 and Standard 3 as well as the deviant stimuli i.e. Standard 3 vs. Pitch change of vowel or Standard 3 vs. Vowel change. In the low (20-48Hz) and high (52-70Hz) gamma ranges to avoid 50Hz line noise as well as 3-6Hz for the theta frequency range.

4.2.1.2.2. *Induced power* will be extracted for the respective conditions 350-600ms post-stimulus onset in both theta 3-6Hz and low (20-48Hz) and high (52-70Hz) gamma ranges. Differences will be examined between Standard 1 and Standard 3 as well as Standard 3 and the deviant stimuli i.e. Pitch change of vowel and Vowel change.

4.2.1.2.3. *Inter-trial phase coherence (ITPC;* measure of phase consistency over trials*)* will be derived from individual trials in the theta (3-6Hz), low (20-48Hz) and high (52-70Hz) gamma ranges frequency ranges. Strength of phase-locking, i.e. degree clustering of phase-angles over trials, will be compared across ages and sub-groups as total phase-locking value for Standard vowels (total ITC values of Standard 1-3) to increase trial number and improve stability of the ITC response. ITC to deviant tones will not be examined due to small trial numbers.

4.2.2. Behavioural

Mullen Scales of Early Learning (29) were administered for every participant at every time point to assess the overall cognitive and motor ability by a team of researchers with years of experience working with infant populations. In the analysis, specific attention will be allocated towards Expressive and Receptive Language sub-scales. From parent report measures, scores on the Negative Affectivity Scale and the Perceptual Sensitivity Subscale Infant Behaviour Questionnaire Revised (IBQ-R) Shortened version (24,30), as well as the total number of words Understood & Said declared on the CDI at 14 months of age (25).

4.2.3. Possible covariates

The initial covariates considered were age (in days) and sex. Groups are not expected to vary significantly on these measures at each visit. For each measured variable, we will test for a possible linear relationship of age/sex and/or an interaction of age/sex with group (i.e. the three time points). We hope to retain as many families as possible throughout the study, so that there will be a comparable number of males and females. If an effect of the covariate is found, it will be included as a covariate in supplementary analyses.

4.3. Indices

4.3.1. Neural

See Appendix 1 for details on filtering, automatic and manual artefact detection. Based on previous work ERPs will be derived through averaging of the signal and power metrics will be calculated through time-frequency decomposition of the EEG signal using the wavelet method (10). The following aspects of the signal will be examined:

4.3.1.1. ERP analysis

4.3.1.1.1. *Habituation*. Grand average voltage of the waveform will be calculated for each Standard (1,2,3) from the clean trials and visualised per ROI. Habituation effects will then be examined by comparing responses across the three standards (50-200ms). Highest responses are expected at the fronto-central sites are selected based on significant findings from child and infant speech perception (32,33), as well as tempo-parietal sites to compare differences between time and time-frequency EEG (23).

4.3.1.1.2. *Change detection* - similarly to the habituation response, grand average waveforms will be calculated for the Pitch and Vowel deviant conditions. These responses will be compared to the response from Standard 3 vs. the Deviants for across two time

windows, 50-200ms and 250-400ms post-stimulus onset.

4.3.1.2. Power analysis:

4.3.1.2.1. *Evoked gamma power* - reflects event related changes in EEG power and calculated by averaging event-locked EEG epochs, where only the frequencies that are phase synchronised to the stimulus survive the averaging (50-300ms). In supplementary analyses, we will further explore individual variability in latency of this response by identifying the highest peak of evoked gamma/theta activity per individual, defined as an area of 3+ consecutive 50ms bins between 50 and 300ms (20-48Hz, 52-70Hz and 3-6Hz).

4.3.1.2.2. *Induced gamma power* - overall changes in EEG power across stimuli (not time-locked). These will be compared between Standard 1 and Standard 3 as well as Sum of Standards vs. Pitch or Vowel change deviants in gamma and theta range 350-600ms.

4.3.1.2.3. *Inter-trial phase coherence (ITPL)* - event-related phase-locking will be used as a measure of neural synchrony (31). Time region of interest will be identified from the whole sample as the largest area of consecutive significant ITC between 0 and 500ms post-stimulus onset by measuring the number of bins with significant ITC values within each age group in the theta and low and high gamma frequency ranges. Identifying the temporal region of interest separately at 5 and 10 months will allow us to examine potential developmental changes in latency of cortical phase synchrony through changes in ITC.

4.3.2. Behavioural

EEG-based neural markers which show significant habituation/change detection responses will be examined in relation to experimenter observations and parent report measures of infant behaviour and cognition. The indices (EL and RL on the Mullen, Negative Affectivity scale and Perceptual Sensitivity subscale on the IBQ-R) will be correlated with these markers to look at whether age-related differences in ERPs or wavelet power are predictive of the behavioural and language phenotype.

5. Design Plan

5.1. Study type

Observational - data is collected from participants who were not randomly assigned to a treatment

5.2. Blinding

Behavioural coding and EEG data cleaning is completed blind to demographic information about the infants.

5.3. Study design
Longitudinal study, data discussed here is from the 5 and 10-month time points.

5.4. Randomisation
N/A

6. Analysis Plan

6.1. Statistical models
Age and group-based differences in chosen EEG indices will be examined using a General Linear Model (GLM). The dependent variables for the models will be average amplitude of selected early and late evoked components, evoked and induced gamma and theta power as well as ITC, with age (in days) and Sex as fixed effects. This method will allow for missing data, which is prevalent to longitudinal research. If the model returns a significant effect of age, analyses will be repeated with number of trials as a covariate.

The role of behavioural measures

6.1.1. For all above analyses age (in days) and sex are included as covariates. Because all infants were tested in a 3-week time window around the 5 and 10 months of age, we do not expect significant effect of age on any of the variables. No predictions are made on the effects of sex.

6.1.2. Due to the exploratory nature of this study, and its aim to inform future research as to key neural measures of specialisation and auditory expertise, no corrections for multiple testing will be made. However, effect sizes will be reported throughout to demonstrate the magnitude of effects and how that changes developmentally.

6.2. Inference criteria
Hypotheses will be tested using two tailed tests at alpha significance level of .05

6.3. Data exclusion
Data that meets the following criteria in pre-processing stages will be considered invalid and excluded from further analysis:

Neural oscillatory (EEG) responses will be subject to several stages of cleaning, including filtering, artefact detection, channel replacement and baseline correction. For each condition, there should be at least 30% good trials retained. Also, the dataset should have at least 30% of good trials from the total administered.

6.4. Missing data
For each significance test, infants with any valid data for a measure will be included, irrespective of whether they have data for the other measures in the protocol. Generalised Linear Models allow to make inferences with missing data.

6.5. Exploratory analyses

In order to understand the nature of difference between groups, we further compare differences in peak latencies (i.e. onset time until maximum response) between age points and participant groups.

To understand if there is any influence of early language input, we will look at two subgroups within the typically developing control group (i.e. based on level of language experience in the home environment). This analysis will constitute follow up t-test to see if the ERP/power findings were significantly different in infants from English-only households than those with additional language experience (ALE) in the home environment. Note that levels of experience are not controlled (but have to be at least 30% English) only 14 infant

7. Appendices

Appendix 1

Auditory trains task

This task was composed from trains of vowel sounds, where three repetitions of the sound /u/ were followed with either a pitch change of /u/ or a vowel change to /i/ (See Figure 1 below) with a 500 millisecond inter-stimulus interval. Order of pitch or vowel change sounds at the end of the auditory trains was randomised.

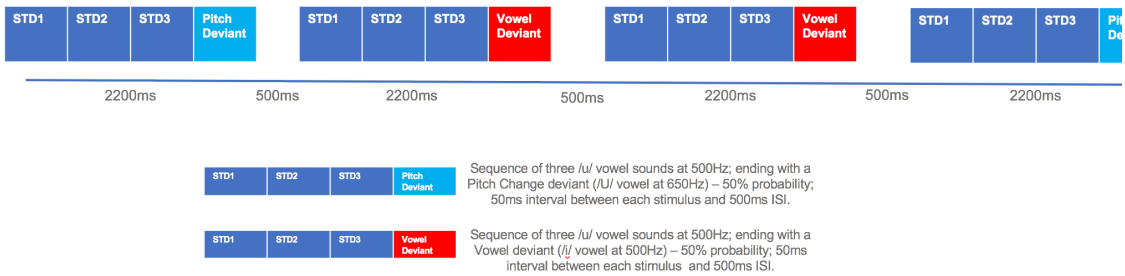


Figure 1 – Details of paradigm for auditory trains task, adapted from Dehaene-Lambertz and Baillet (1998) and Guiraud and colleagues (2011).

Pre-processing and data cleaning

Raw EEG data files will be pre-processed in Netstation (Version 4.5.7). The steps that will be involved in this analysis are:

1) *Filtering* – The data will be filtered offline with a 0.1Hz high pass and a 100Hz low pass filter. Any recording below 0.1Hz are likely to be skin or movement potentials and above 100Hz to be gross movement artefact and thus not brain activity. A fairly liberal range is to be retained as we are interested in higher frequency oscillatory activity. Line noise present in the data is addressed by [1] a 50Hz notch filter and [2] elimination of 49-51Hz data from statistical analysis.

2) *Segmentation* – Data will be segmented -100ms before and 800ms after stimulus onset to examine the exact neural activity following presentation of the vowel sounds. The resultant 5 categories of segments are: Standard 1, Standard 2, Standard 3, Pitch Change, Vowel Change. Note that stimuli within a train occur every 500ms, which means that the segments will overlap with the next stimulus. However, this is done to ensure sufficient segment length for wavelet analysis where smearing occurs at the edges.

3) *Baseline correction* – All newly created epochs will then be baseline corrected to examine the neural activity associated with stimulus onset rather than general neural activity that fluctuates over temporal and spatial regions. This will be done by taking an average of neural activity that occurs pre-stimulus presentation and subtracting it from entire waveform length after stimulus onset. For Event Related Potential (ERP) analysis, 100ms baseline is considered appropriate (34,35), however, this will be increased to 200ms in present analysis due to temporal smearing characteristic of wavelet analysis (36).

4) *Automatic artefact detection* – The main artefacts of concern are blinks, eye-movements (saccades), movement potentials and alpha activity, which are much more prevalent in infant than adult EEG data (37,38). For the present analysis, some simple filters will be used to identify potentially 'bad' trials/or channels to increase speed of manual cleaning (all part of tools available through Netstation).

a. EOG filter – detects blinks. Uses two criteria 1) samples outside critical SDs from the mean voltage across the trails and 2) channels which fit a second order polynomial curve above 0.6, which would detect drift across the channel that is typically associated with eye movement.
b. Eye movement - detects changes over 55μV in a 640ms time window and marks those channels as bad.
c. Bad channels – this is a basic filter which finds channels with absolute voltage that exceed the min/max criterion (below 0.1μV or above 200μV on any EEG channel) will be rejected from further analysis.

5) *Manual cleaning* – the data will then be visually inspected and marked for artefacts either by marking a bad channel or a whole trial. This will be used to correct any under/overestimations from the automatic detection filters. A trial with over 25 bad channels or a cluster of 15 channels in one region will be marked as 'bad' and not included in further analysis. *ƒ*standΩ

6) *Bad channel replacement* – once artefact-detected data will be exported from the visualisation tool, channels marked as 'bad' will be interpolated by an average voltage value of the neighbouring electrodes. This will be done on a per-trial basis to preserve a high number of trials.

7) *Re-referencing* – pre-processed signal will be re-referenced to the average reference. This is the average of neural activity from all 129 sensors (128 electrodes + vertex) and has been deemed appropriate for high-density arrays (39).

9) *ERP analysis* - grand average waveforms will be calculated by averaging all individual datasets within a condition over segment time, which will produce 5 average datasets (Standard 1, 2, 3, Pitch Deviant, Vowel Deviant) in both groups.

10) Latency analysis (exploratory) – from the grand average signals for each participant, positive/negative response the latency of the point where the amplitude of the response falls in the 50% of the maximum amplitude of the grand averaged waveform (averaged over participant groups and conditions). This value was calculated for each participant, and then the minimum and maximum values were taken as upper and lower ends of the temporal

window of interest. Amplitudes were then calculated as the mean voltage within each latency window.

After this, the data is exported into Matlab (Version R-2017a) via the EEGLAB toolbox (v.13.6.5b, http://sccn.ucsd.edu/eeglab/) for the last steps of the analysis. Wavelet calculations and ERPs are extracted using the Fieldtrip toolbox (26).

11) *Averaging* - for analysis of evoked power and ERPs, individual averaging will be performed. During this step, remaining 'good trials', those not rejected during artefact detection, are combined together to produce a composite waveform per condition per infant. A grand average of all trials per condition is then computed from all participants in an age group for time and time-frequency analyses. For induced power analysis, averaging is performed after wavelet transformation.
12)*Wavelet transformation* - time-frequency analyses will be carried out with a continuous wavelet transform using Morlet wavelets (36,40). Wavelets will be constructed 20-80Hz with a 1Hz interval. Wavelet cycles is set at 3.5 (i.e. the overlapping time window will begin with a 3.5 cycle wavelet with a Hanning-tapered window applied). Raw pre-processed EEG signal will then be convoluted with the wavelet and taking the modulus of the result. Induced activity will be calculated by applying the transform to all EEG signals recorded at each channel and for each trial, and then averaged together. Evoked activity is calculated by applying the transform to the average of all EEG signals across trials to isolate frequency responses time-locked to presentation of the stimulus.

Identifying spatial ROIs (Figure 2) – For present analysis of vowel sounds, central scalp regions will be selected for statistical comparisons as previous investigations found strong MMN effects in electrodes around the frontal and central scalp area in infants (22,41). Additionally, bilateral frontal and tempo-parietal regions will be included in present analysis as robust evoked responses in the gamma and theta range have been localised in the study of typical and atypical auditory perception (10,41–43; see electrode locations highlighted in Figure 2). Note that although several investigations report frontal gamma activation in auditory processing (45,46), results from this region will be interpreted with caution due to high possibility of oculomotor artefact interfering with final power calculation (47).
Note that if we do not observe significant effects of Condition within the typically developing control group, but the effects are visible in the grand average plot of all electrodes, these regions will be explored in supplementary analyses.

Identifying temporal ROIs - For this analysis, temporal regions of interest are defined based on previous work (see indices outlined above) as well as grand average summary of ERP power 0-800ms, which helped to identify the biggest positive/negative peak following stimulus onset. While this allows us to reduce the number of comparisons and thus the likelihood of obtaining a Type 1 error, there may be temporal regions in the data which are not covered as well as limit our understanding of differences in onset of responses which may be driven by age and/or group status.

Dependent variables:
General output (for each participant in each age group). Note that the time/frequency range will depend on variable measured and are not consistent for each measure.

1) ERPs: amplitude of grand averaged ERP for: Standard 1, 2, 3, Pitch Deviant, Vowel Deviant stimuli at Frontal Right, Frontal Left, Central, Tempo-Parietal Right, Tempo-Parietal Left clusters). Responses will then be defined based on the hypothesis:

a. Habituation – Standard stimuli 1-3 (50-200ms)
b. Change detection – Pitch Deviant minus Standard 3; Vowel Deviant minus Standard 3 (250-400ms)

2) Evoked gamma: time-frequency matrices calculated from segmented averaged EEG datasets. The data will be averaged by condition: Standard 1, 2, 3, Pitch Deviant, Vowel Deviant (3-6 Hz, 20-48Hz, 52-70Hz; over 50-300ms).

3) Induced gamma: time-frequency matrices calculated from individual trials, then averaged across datasets. The data will be averaged by condition: Standard 1, 2, 3, Pitch Deviant, Vowel Deviant (3-6 Hz, 20-48Hz, 52-70Hz; over 350-600ms).

4) Inter-trial coherence: ITC values (single vectors per trial) will be extracted using an EEGLAB function on un-averaged segmented files for all participants together in the theta, low and high gamma ranges between 0 and 600ms (in 10ms segments). The largest area of significant ITC will then be identified for further analyses (as measured by the number of bins with significant ITC values - i.e. the Peak ITC value). If another area of significant ITC with more than 3 bins was within 20ms of the first, it will be included in the measured area. Standard 1-3 only will be averaged together and analysed here as ITC requires large amounts of trials to produce a stable response (Cohen, 2014). Comparisons will be run across age and participant group.

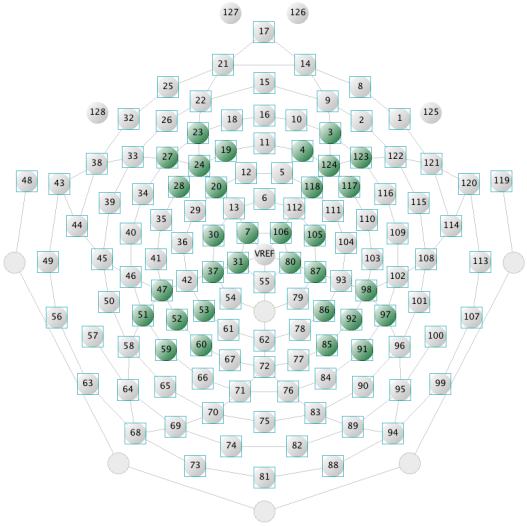


Figure 2 - Location of electrodes used in statistical analyses of the auditory trains task illustrated on the 128-channel HydroCel GSN. Names given approximate the 10-10 layout. Electrodes outlined in green represent clusters used in analysis (Frontal Right (3,4, 118, 124, 123, 117) and Left (27, 23, 28, 24, 19, 20), Central Right (106, 80, 105, 87) and Left (30, 37, 7, 31), Tempo-Parietal Right (86, 85, 92, 98, 91, 97) and Left (51, 47, 59, 52, 53, 60). Note that grand average waveforms will be visualised for the whole layout and significant ROIs not defined here will be discussed in supplementary analyses.

Parameters to co-vary

1) Number of valid trials (per condition)
2) Age (in days)
3) Sex

Statistical analyses

Linear mixed models will be used as the main type of analysis due to presence of missing data across the two visits, with Group (TD, NF1), Age Point (5, 10 months) as fixed factors and sex and age (in days as co-variates). Type III Sums of Squares was used to account for unequal group comparisons. Levene's tests for equality of variances will be used to determine if there are significant differences in homogeneity of variances in each infant group.

1) ERP responses
    a. Habituation - A LMM will be used to compare total amplitude 50-200ms between first and third repetition of the standard from chosen ROIs with Age as a fixed factor.
    b. Mismatch negativity – A series of LMMs will be run to compare total amplitude 250-400ms change between [1] Sum Standard 1-3 and Pitch deviant and [2] Sum Standard 1-3 and Vowel deviant with Age as a fixed factor.
2) Power analysis
    a. Evoked power (theta and gamma-band responses)
        i. Habituation – LMM to compare differences in evoked power of AOI Standard 3 minus Standard 1 with age (5 and 10mo) as a fixed effect and sex as a random factor.
        ii. Change detection – LMM to compare differences in evoked power of AOI between Vowel Change and Pitch Change effects with age (5 and 10mo) as a fixed effect and sex as a random factor.
    b. Induced power (theta and gamma-band responses)
        i. Habituation – LMM to compare differences in induced power of AOI Standard 3 minus Standard 1 with age (5 and 10mo) as a fixed effect and sex as a random factor.
        ii. Change detection – LMM to compare differences in induced power of AOI between Vowel Change and Pitch Change effects with age (5 and 10mo) as a fixed effect and sex as a random factor.
    c. Inter-trial coherence
        i. Identifying AOI across all Standards for time region of phase-resetting 0-500ms (in 10ms increments) for 3-6Hz and 20-48 and 52-70Hz bands. Peak ITC, range of ITC in milliseconds, and range in Hz will be treated as dependent variables.
        ii. A series of LMMs will be carried out to compare differences between ITC for all Standards collapsed, group and age point (5 and 10mo) as a fixed effects and sex and age (days) as random factors.

3) Behavioural correlations – age-dependent EEG-correlates will be compared to [1] standardised scores on Expressive Language and Receptive Language subscales for all infants on the Mullen [2] Scores on the Negative Affectivity Scale on the IBQ-R (comprised of the subscales Sadness, Distress to Limitations, Fear and Falling

Reactivity/Rate of Recovery from Distress as well as the Perceptual Sensitivity subscale. Lastly, [3] EEG indices will be correlated with the total number of words Understood and Said on the CDI.

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Appendix H. *Analysis of EL-Atyp group.*

The following section described the additional analyses from the EL-Atyp group, which were not included as part of the main analysis in order to increase power.

Habituation analysis:

Firstly, a univariate ANOVA was run to look at the differences in 40-60Hz evoked gamma amplitude between Standard 3 and Standard 1. The difference was significant across groups ($F(2, 74)=4.18$, $p=.019$, $\eta^2=.102$), and remained significant after controlling for Trial number ($F(2,74) = 4.21$, $p = .019$, $\eta^2=.104$). Specifically, the EL-Atyp group showed a decrease in gamma activation between the 1st and 3rd repetition (similar to EL-TD group and in contrast to the increase reported in the EL-ASD group). Pairwise comparisons showed that this difference was significantly higher in EL-ASD infants than EL-TD ($p=.012$) and EL-Atyp ($p=.008$) groups (see Figure F1).

Next, I compared ITC responses to all Standard tones. The ANOVA did not return significant ITC differences between the three outcome groups (EL-TD, EL-Atyp, EL- ASD), ($p=.157$; $p=.179$ with trial numbers co-varied). It can be seen in Figure F2that the EL-Atyp group had higher ITC relative to infant siblings who were typically developing, however, future experiments will need to incorporate high trial numbers to explore this possibility.

As highlighted in the main text of the chapter, the EL-Atyp group was included in analysis of the composite cortical hyper-reactivity scores, where higher scores on the scale indicated diminished auditory habituation (Figure 5.3 in the main text). The ANOVA revealed a significant main effect of group when all EL groups were included ($F(3,85)=3.68$, $p=.015$, $\eta^2=.115$), and also when number of trials is co-varied ($F(3,84)=3.64$, $p=.016$, $\eta^2=.115$). Pairwise comparisons showed that infants with later typical development had significantly lower CRI scores relative to EL-ASD group ($p=.002$) controlling for Trial number.

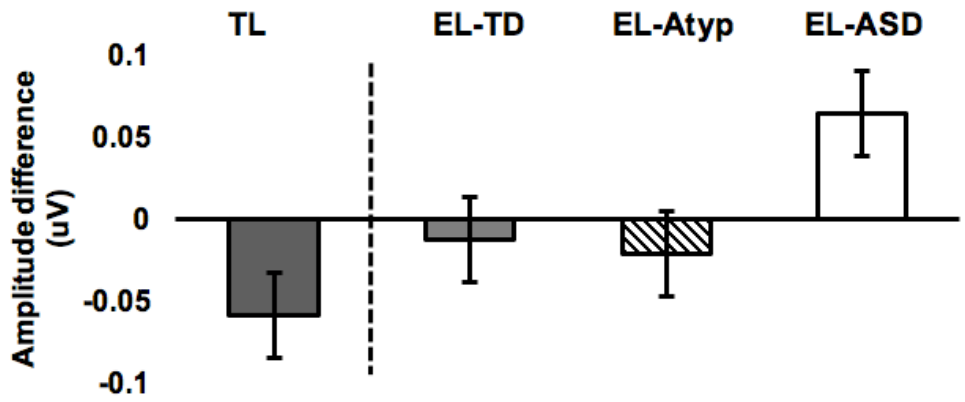

Figure F1. Amplitude difference of 40-60Hz evoked gamma in the right tempo-parietal electrodes between Standard 3 and Standard 1for all four groups in the sample. TL group is included for reference of a typical repetition suppression response, but not included in the statistical comparisons.

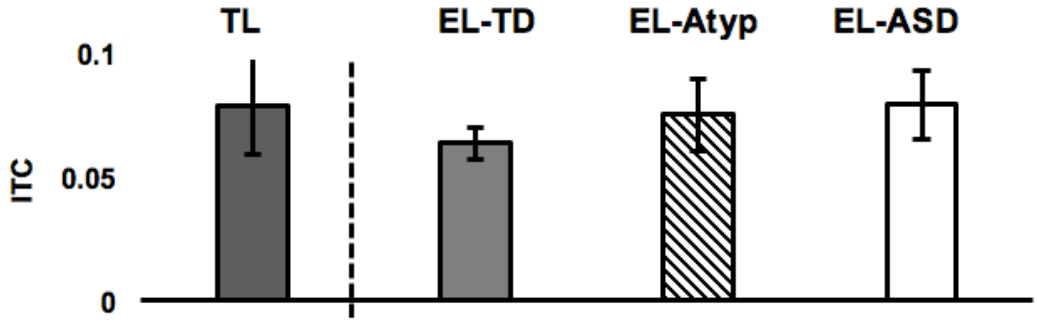

Figure F2. Intertrial coherence (ITC) values for all groups for all standards collapsed. The group effect remained after EL-Atyp group was added. TL group included for reference.

Change detection analysis:

Gamma responses to Deviants were then compared for the EL-Atyp group. As no differences were found for either deviant stimulus, both were entered into the analysis. A univariate ANOVA for responses to the Pitch Deviant did not reveal a main effect of group, with or without trial numbers included in the analysis [all ps>.5]. Similarly, no differences were observed for responses to the White Noise deviant in either gamma band.

Appendix I. *Clinical assessment.*

A battery of clinical research measures was administered to all children at 36 months (see Table G): the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2;(Lord et al., 2000)), a standardised interaction observation assessment, was used to assess current symptoms of ASD (116 children were administered Module 2 and 20 children Module 1, ADOS not completed with 5 EL and 2 TL children). Calibrated Severity Scores for Social Affect, and Restricted and Repetitive Behaviours (RRB) were computed (Gotham et al., 2009), which provided standardised autism severity measures, which accounted for differences in module administered, age and verbal ability. The Autism Diagnostic Interview – Revised (ADI-R; (Rutter, Le Couteur, et al., 2003), a structured parent interview, was also administered. Standard algorithm scores were computed for Reciprocal Social Interaction (Social), Communication, and Restricted, Repetitive and Stereotyped Behaviours and Interests (RRB). These assessments were conducted without blindness to group status by or under the close supervision of clinical researchers (i.e., psychologists, speech therapists) with demonstrated research-level reliability. Total scores of the Social Communication Questionnaire (SCQ; (Rutter, Bailey, et al., 2003) were used as additional parent report measures of ASD symptoms. The early learning composite scale score of the Mullen Scales of Early Learning (MSEL; (Mullen, 1995) was used to obtain a standardized measure of developmental abilities during the 3 year visit.

Experienced clinicians (TC, GP, CC) reviewed information on ASD symptomatology (ADOS-2, ADI-R, SCQ), adaptive functioning (Vineland-II;(Sparrow, 2011)), and development (MSEL) for each child to ascertain ASD diagnostic outcome according to DSM-5 (American Psychiatric Association, 2013). From the 113 EL participants with sufficient EEG data for analysis, 17 (15 boys, 2 girls) met criteria for ASD (EL-ASD). From the remaining 96 participants (48 boys, 48 girls), infants were either typically developing (28 boys, 36 girls; EL-TD) or atypically developing (20 boys, 12 girls; EL-Atyp) at 36 months. None of the 25 TL children (14 boys, 13 girls; RL) met DSM-5 criteria for ASD and none had a community clinical ASD diagnosis.

For 111 of 116 children with an older sibling with a community clinical diagnosis of ASD (EL groups, hereafter probands), parents had completed the Development and Wellbeing Assessment (DAWBA; Goodman et al., 2000) and/or the Social Communication Questionnaire (SCQ; Rutter et al., 2003). Seventy-seven probands met criteria on both the DAWBA and SCQ. While a small number scored below threshold on the SCQ (n = 8), no exclusions were made due to meeting threshold on the DAWBA and expert opinion. For 19 probands, confirmation of local clinical diagnosis was only available for the SCQ. For 5 probands, neither measure was available aside from parent-confirmed community clinical ASD diagnosis. Screening for possible ASD in the older siblings of the TL infants was undertaken using the SCQ, with no child scoring above the instrument cut-off for ASD (>15) (one missing). Medical history review confirmed a lack of ASD within first-degree relatives.

Table G. *Detailed characterization all behavioural assessments completed by the EL subgroups and TL controls at all visits for all participants that contributed data to the present analysis at the 8 and 36months visit.*

	EL-ASD	***EL-Atyp***	***EL-TD***	***TL***
8 months				
Age in months (SD)	8.83 (.82)	8.9 (.69)	9.10 (.84)	9.29 (.84)
MSEL Receptive Language	47.4 (8.9)	49.11 (7.3)	50.98 (9.65)	49 (11.05)
MSEL Expressive Language	55.87 (12.41)	53 (11.08)	54.64 (9.4)	57.64 (9.3)
N (% boys)	14 (88.24%)	21 (65.5%)	44 (43.75%)	14 (51.85%)
36 months				
Age in months (SD)	38.56 (1.71)	38.69 (1.87)	38.84 (1.60)	38.72 (1.62)
MSEL Receptive Language	39.6 (16.5)	44.11 (14.78)	56.91 (9.17)	59.08 (9.5)
MSEL Expressive Language	38.53 (16.05)	45.63 (12.7)	57.02 (10.44)	60.42 (11.3)
SRS™ Total t-scores	92.87 (31.82)	42.14 (30.73)	29.28 (22.2)	21.28 (10.34)
ADI-Social	12.13 (5.76)	3.06 (3.16)	2.00 (2.55)	0.96 (1.49)
ADI-Communication	11.50 (4.69)	4.44 (4.25)	2.62 (3.29)	0.48 (1.05)
ADI-RRB	5.63(2.55)	1.25 (2.15)	1.49 (2.57)	2.56 (1.96)
ADOS-Total	8.81 (7.68)	8.13 (4.79)	2.44 (1.63)	3.68 (3.09)

MSEL – Mullen Scales for Early Learning (t-scores); SRS™ - Social Responsiveness Scale; ADI – Autism Diagnostic Interview; ADOS – Autism Diagnostic Observation Scale (Calibrated Severity Score).

Individual t-scores on the Expressive and Receptive Scales (Mullen, 1995) were entered into a repeated measures ANOVA to look at group differences in age of testing and the scores. The model revealed a significant main effect of Group ($F(1,86)=10.05$, $p<.001$, $\eta^2=.26$), as well as an interaction between Age and Group ($F(3,86)=9.01$, $p<.001$, $\eta^2= .24$). Means tables suggested that while there was an increase in Expressive and Receptive language scores in the TL and EL-TD groups between 8 and

36 months, infants with later ASD or atypical development showed a worsening in their performance on these scales over time.

SRS™ total *t*-scores were entered into a one-way ANOVA and revealed a significant effect of Group ($F(3,124)=33.12$, $p<.001$, $\eta^2 =.44$). Infant siblings with later ASD had higher scores on Social Responsiveness Scale (which measures presence and extent of autistic social impairment).

A multi-variate ANOVA was run to look at differences in ADI and ADOS behavioural scales between groups at 36 months. As predicted, all *p* values were under the significance threshold of 0.05, which suggested that the EL-ASD group was rated higher on all symptomatic aspects of ASD-related symptoms relative to the typically developing infants (EL-TD).

Appendix J.*Microsaccades analysis (Habituation only).*

The effect of ocular artefacts on the measures used in the present study were examined based on a recently published analysis (Kampis et al., 2016). To eliminate the possibility of that the observed effect of enhanced gamma activity following tone repetition in the EL-ASD group were due to co-occurring micro saccades (MS) of the eyes, the bipolar horizontal EOG signal from the channels closest to the eye area (channel 32 subtracted from channel 1) was compared with gamma habituation. Each outcome group was analysed separately due to the possibility of atypical MS in ASD relatively to the typically-developing controls (Schmitt et al., 2014). The 40-60Hz evoked responses were compared between the change between 1st and 3rd standard in the right tempo-parietal scalp region and the difference in EOG signal between these two stimuli. The correlation was non-significant for (1) TL group ($r(13)=.266$, $p=.358$, *CI*[-0.28 0.68]) and EL-TD ($r(43)=-.005$, $p=.975$, *CI*[-0.28 0.29]), and (2) EL-TD and EL-ASD ($r(12)=.148$, $p=.629$, *CI*[-0.41 0.62]) groups. Pearson's product moment correlation showed no association between gamma habituation difference score and EOG signal ($r(71)=-.054$, $p=.653$, *CI*[-0.68 -0.35]) across the three groups combined (see Figure H1). Ocular artefact analyses were not repeated for deviant stimuli as no group effects were observed.

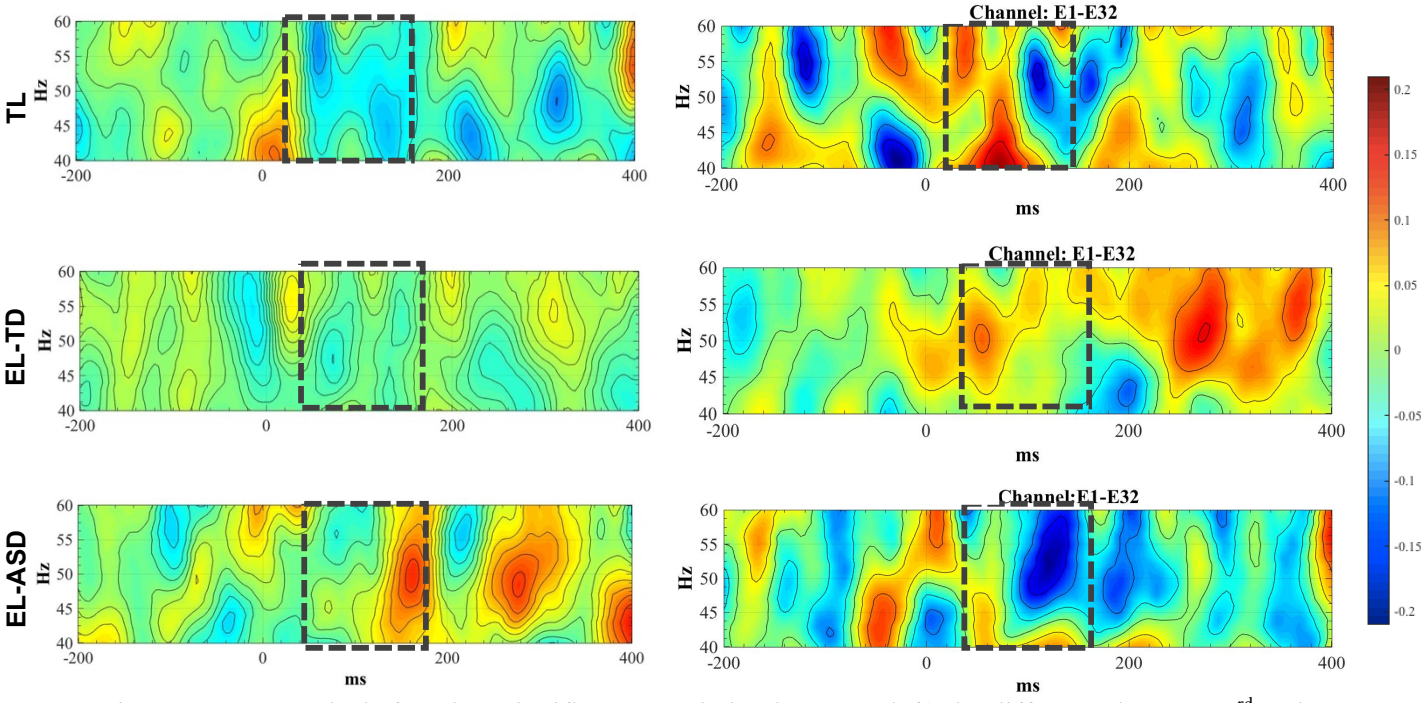

Figure H1. MS analysis found no significant association between (left) the difference between 3rd and 1st repetition of the standard tone and (right) differences in the eye channel data (channel 32 subtracted from channel 1; Standard 3 – Standard 1). Dashed rectangles mark the window of interest.

Appendix K. *STAARS diagnostic information.*

Information regarding diagnostic status was ascertained through a number of methods. Before families enrolled in the study, a telephone screening form was used to determine the presence of ASD and ADHD in family members. At the infant's 10 month (or first) visit to the lab site, the parent/caregiver also completed a "Medical and Psychiatric History Interview" with the researcher. The telephone screening form and this formal interview at study intake were the primary source of information about diagnostic status prior to standardised assessments during follow-up visits. In addition, we asked for medical updates at each study visit and re-administered the Medical and Psychiatry History Interview at the 3-year time point. The testing team also requested diagnostic letters and asked parents to complete the DAWBA (Goodman et al., 2000) ASD and ADHD sections and these were reviewed by the senior clinician (Prof Tony Charman). In addition, parents completed the Conners (For ADHD Conners, 2009) and the SCQ and SRS (for ASD; Constantino, 2012; Matthey, 2001) on the family member with a diagnosis and where possible all other family members.

This information is used to characterise our sample rather than to be used for exclusionary purposes; since in the UK NHS clinical diagnoses follow a gold-standard procedure including collation of information from parents, teachers and from in-person assessment that is beyond the scope of this study and more accurate than simple questionnaire measures. Up to 30% of children with ASD meet criteria for ADHD when prospectively assessed (Simonoff et al., 2008). In clinical practice, the prevalence of dual diagnosis is in practice much lower (Russell et al., 2014). Given the nature of the co-occurrence between ASD and ADHD and our longitudinal study, sometimes family members would have a suspected diagnosis of ADHD at study entry that would be confirmed later in the study; on other occasions, a family would enrol on the basis of an ASD diagnosis in an older sibling but by the end of the study, they would report that the same sibling was now undergoing assessment for suspected additional ADHD. Where possible, families who reported suspected ADHD at study entry were screened using a shortened version of the Conners. Families who screened positive on this instrument were then included as a confirmed case. However, it remains likely that within families with ASD, rates of actual ADHD are higher than those captured by our 1/0 diagnostically-based rating system.

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